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PCT/EP2005/004422

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South Wales NP10 8QQ

1.	Your reference	4-33739P1
2.	Patent application number *(The Patent Office will fill in this part)*	0409236.7 — 26 APR 2004
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	NOVARTIS AG LICHTSTRASSE 35 4056 BASEL SWITZERLAND
	Patent ADP number *(if you know it)*	7125487005
	If the applicant is a corporate body, give the country/state of its incorporation	SWITZERLAND
4.	Title of invention	Organic Compounds
5.	Name of your agent *(If you have one)*	Craig McLean
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	Novartis Pharmaceuticals UK Limited Patents and Trademarks Wimblehurst Road Horsham, West Sussex RH12 5AB
	Patents ADP number *(if you know it)*	07181522002 ✓

6.	If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of filing (day/month/year)

7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (day/month/year)

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   a) *any applicant named in part 3 is not an inventor, or*

   b) *there is an inventor who is not named as an applicant, or*

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Description	77
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Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	1
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11. I/We request the grant of a patent on the basis of this application

Signature Date

Craig McLean 26th April 2004

12. Name and daytime telephone number of person to contact in the United Kingdom

Mrs S Schnerr 01403 323069

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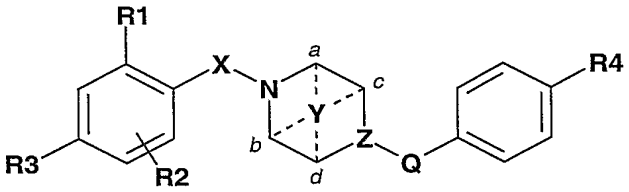
DUPLICATE

Organic compounds

This application relates to bicyclic piperazines and piperidines that are antagonists of Chemokine Receptor 1 (CCR-1) and to their use in the treatment of diseases or disorders that involve migration and activation of monocytes and T-cells, including inflammatory diseases.

Accordingly the application provides a compound of formula I, or a pharmaceutically acceptable salt or ester thereof,



I

wherein

R1, R2 and R3 are independently selected from the group consisting of hydrogen, cyano, halo, nitro or optionally substituted oxy, lower alkyl, lower alkyenyl, lower alkynyl, carbonyl, amino, sulfur, cycloalkyl, heterocycloalkyl, aryl, heteroaryl or a substituent forming a bicyclic ring system of which the phenyl ring to which it is attached forms part of the bicycle for example butadiene forming napthyl, or heterobutadiene forming quinolinyl, quinoxalinyl or isoquinolinyl;

R4 is selected from the group consisting of hydrogen, cyano, halo, nitro or optionally substituted oxy, lower alkyl, lower alkyenyl, lower alkynyl, carbonyl, amino, sulfur, cycloalkyl, heterocycloalkyl, aryl, heteroaryl or a substituent forming a bicyclic ring system of which the phenyl ring to which it is attached forms part of the bicycle for example butadiene forming napthyl, or heterobutadiene forming quinolinyl, quinoxalinyl or isoquinolinyl;

X is $-CH=CHCO-$, $-OCH_2CO-$ or $-NHCH_2CO-$;

Y is $-(CH_2)_n-$ where n is 1-6, $-CH_2OCH_2-$ or $-CH_2NRCH_2-$ and is bonded to two of the ring carbon atoms, bonding being to either the ring carbon atoms *a* and *b* or the ring carbon

atoms *c* and *d*; wherein R is selected from the group consisting of H, optionally substituted: lower alkyl, carbonyl, acyl, acetyl or sulfonyl;

Z is N or –CH-;

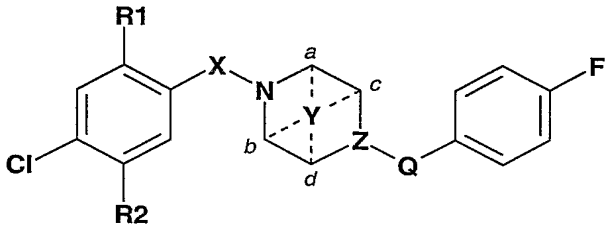
Q is $-CH_2-$, -NH- or -O-;

wherein when Z is N, Q is CH_2, and when Z is –CH-, Q is –NH- or –O-;

with the proviso that when Y is $-(CH_2)_n-$ and when Z is N, X is –CH=CHCO-;
and the proviso that when Q is NH or O and when X is $-OCH_2CO-$ or $-NHCH_2CO-$ and when Y is $-(CH_2)_n$ or $-CH_2OCH_2-$, Y is bonded to ring carbon atoms *c* and *d*.

The optional substituents on R1-R4 are one or more, e.g. 1-3 substituents, independently selected from the group consisting of hydrogen, oxo, cyano, halo, nitro or optionally substituted oxy, lower alkyl, lower alkyenyl, lower alkynyl, amino, sulfur, sulfinyl, sulfonyl; wherein the optionally substituted substituents are optionally substituted once or more by, e.g. 1-6 substituents, a substituent independently selected from the group consisting of hydrogen, oxo, cyano, halo, nitro, oxy, lower alkyl, lower alkyenyl, lower alkynyl, amino, sulfur, cycloalkyl, heterocyloalkyl, aryl.

The invention further comprises a compound of formula II:



II

wherein R1, R2, X, Y, Z and Q are as defined above with respect to formula I.

With respect to the compounds of the invention, preferably, R3 is halo. More preferably it is Cl. Preferably, R4 is halo. More preferably it is F. Preferably n is 2 or 3.

According to the invention in a second aspect, there is provided a compound of formula I wherein the compound includes a radioisotope selected from the group of ^{11}C, ^{18}F, ^{75}Br, ^{76}Br, ^{80}Br, ^{123}I, ^{125}I, ^{128}I, ^{131}I, ^{13}N , ^{15}O.

Above and elsewhere in the present description the following terms have the following meaning:

The term "lower" in connection with organic radicals or compounds means a compound or radical which may be branched or unbranched with up to and including 7 carbon atoms.

A lower alkyl group is branched or unbranched and contains from 1 to 7 carbon atoms, preferably 1 to 4 carbon atoms. Lower alkyl represents for example methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, n-pentyl, t-butyl, n-heptyl. Lower alkyl is optionally substituted by hydrogen, cyano, halo, nitro, amino, oxy, alkoxy.

A lower alkenyl group is branched or unbranched, contains from 2 to 7 carbon atoms, preferably 2 to 6 carbon atoms, and contains at least one double bond. Lower alkyenyl is optionally substituted by hydrogen, cyano, halo, nitro, amino. Lower alkenyl represents for example ethenyl, prop-1-enyl, but-1-enyl, pent-1-enyl, pent-1,4-dienyl.

A lower alkynyl group is branched or unbranched, contains from 2 to 7 carbon atoms, preferably 2 to 6 carbon atoms, and contains at least one tripple bond. Lower alkynyl is optionally substituted by hydrogen, cyano, halo, nitro, amino. Lower alkynyl represents for example ethynyl, prop-1-ynyl, but-1-ynyl, pent-1-ynyl, pent-3-ynyl.

Amino relates to the radicals $-NH_2$ and =NH and may be optionally substituted; for instance, by lower alkyl

Aryl represent carbocyclic aryl and heterocyclic aryl.

Carbocyclic aryl represents an aromatic cyclic hydrocarbon containing from 6 to 18 ring atoms. Carbocyclic aryl is mono-, bi- or tricyclic. Carbocyclic aryl represents for example phenyl, naphthyl, biphenyl. Carbocyclic aryl is optionally substituted by up to 4 substituents.

Carbonyl refers to the radical -C(O)-

Cyano or nitrile represents the radical -CN

Cycloalkyl represents a cyclic hydrocarbon containing from 3 to 12 ring atoms preferably from 3 to 7 ring atoms and may be mono-, bi- or tricyclic and includes spiro. Cycloalkyl represents for example cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. Cycloalkyl is optionally substituted.

Halo represents chloro, fluoro or bromo but may also be iodo.

Heterocyclic aryl represents an aromatic cyclic hydrocarbon containing from 5 to 18 ring atoms of which one or more, preferably 1 to 3, are heteroatoms selected from O, N or S. It may be mono or bicyclic. Heterocyclic aryl is optionally substituted. Heterocyclic aryl represents for example pyridyl, indoyl, quinoxalinyl, quinolinyl, isoquinolinyl, benzothienyl, benzofuranyl, benzopyranyl, benzothiopyranyl, furanyl, pyrrolyl, thiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, thiadiazolyl, tetrazolyl, pyrazolyl, imidazolyl, thienyl.

Heterocycloalkyl represents a mono-, bi- or tricyclic hydrocarbon containing from 3 to 18 ring atoms preferably from 3 to 7 ring atoms and contains one or more, preferably 1 to 3, heteroatoms selected from O, N or S. Heterocycloalkyl is optionally substituted. Heterocycloalkyl represents for example pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, indolinylmethyl, imidazolinylmethyl and 2-Aza-bicyclo[2.2.2]octanyl

Nitro represents the radical $-NO_2$

Oxo represents the substituent =O

Oxy represents the radical –O-, and includes -OH

sulfur indicates the radicals –S-, $-\overset{\|}{S}-$ and $\gtrless S \lessgtr$

In particular the invention includes a compound selected from:

(E)-N-(5-Chloro-2-{3-[3-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1]oct-8-yl]-3-oxopropenyl}-phenyl)acetamide

(E)-N-(5-Chloro-2-{3-[3-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1]oct-8-yl]-3-oxopropenyl}-phenyl)-N'-cyanoguanidine

(E)-N-(5-Chloro-2-{3-[3-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1]oct-8-yl]-3-oxopropenyl}-phenyl)-2-dimethylaminoacetamide

(E)-(5-Chloro-2-{3-[3-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1]oct-8-yl]-3-oxopropenyl}-phenyl)-urea

(E)-N-(5-Chloro-2-{3-[8-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1]oct-3-yl]-3-oxopropenyl}-phenyl)acetamide

(E)-N-(5-Chloro-2-{3-[3-(4-fluorobenzyl)-3,9-diazabicyclo[3.3.1]non-9-yl]-3-oxopropenyl}-phenyl)-acetamide

(E)-N-(5-Chloro-2-{3-[3-(4-fluorobenzyl)-3,9-diazabicyclo[3.3.1]non-9-yl]-3-oxopropenyl}-phenyl)-urea

(E)-N-(5-Chloro-2-{3-[3-(4-fluorobenzyl)-3,9-diazabicyclo[3.3.1]non-9-yl]-3-oxopropenyl}-phenyl)-N'-cyanoguanidine

(E)-N-(5-Chloro-2-{3-[3-(4-fluorobenzyl)-3,9-diazabicyclo[3.3.1]non-9-yl]-3-oxopropenyl}-phenyl)-2-dimethylaminoacetamide

N-(5-Chloro-2-{2-[7-(4-fluorobenzyl)-3-oxa-7,9-diazabicyclo[3.3.1]non-9-yl]-2-oxoethoxy}-phenyl)acetamide

N-(5-Chloro-2-{2-[9-(4-fluorobenzyl)-3-oxa-7,9-diazabicyclo[3.3.1]non-7-yl]-2-oxoethoxy}-phenyl)acetamide

(E)-N-(5-Chloro-2-{3-[9-(4-fluorobenzyl)-3-oxa-7,9-diazabicyclo[3.3.1]non-7-yl]-3-oxopropenyl}-phenyl)-acetamide

(E)-N-(5-Chloro-2-{3-[7-(4-fluorobenzyl)-3-oxa-7,9-diazabicyclo[3.3.1]non-9-yl]-3-oxopropenyl}-phenyl)-acetamide

(E)-N-(5-Chloro-2-{3-[7-(4-fluorobenzyl)-3-oxa-7,9-diazabicyclo[3.3.1]non-9-yl]-3-oxopropenyl}-phenyl)-urea

(E)-N-(5-Chloro-2-{3-[7-(4-fluorobenzyl)-3-oxa-7,9-diazabicyclo[3.3.1]non-9-yl]-3-oxopropenyl}-phenyl)-N'cyanoguanidine

(E)-(5-Chloro-2-{3-[9-(4-fluorobenzyl)-3-oxa-7,9-diazabicyclo[3.3.1]non-7-yl]-3-oxopropenyl}-phenyl)-urea

9-[2-(2-Acetylamino-4-chloro-phenoxy)-acetyl]-7-(4-fluorobenzyl)-3,7,9-triazabicyclo[3.3.1]nonane-3-carboxylic acid tert-butyl ester

N-(5-Chloro-2-{2-[3-(4-fluorobenzyl)-3,7,9-triazabicyclo[3.3.1]non-9-yl]-2-oxo-ethoxy}-phenyl)-acetamide

7-[2-(2-Acetylamino-4-chloro-phenoxy)-acetyl]-9-(4-fluorobenzyl)-3,7,9-triazabicyclo[3.3.1]nonane-3-carboxylic acid tert-butyl ester

N-(5-Chloro-2-{2-[9-(4-fluoro-benzyl)-3,7,9-triaza-bicyclo[3.3.1]non-3-yl]-2-oxo-ethoxy}-phenyl)-acetamide

(E)-N-(5-Chloro-2-{3-[3-(4-fluorobenzyl)-3,7,9-triazabicyclo[3.3.1]non-9-yl]-3-oxo-propenyl}-phenyl)-acetamide

(E)-N-(5-Chloro-2-{3-[3-(4-fluorobenzyl)-3,7,9-triazabicyclo[3.3.1]non-9-yl]-3-oxopropenyl}-phenyl)-2-dimethylaminoacetamide

(E)-N-(5-Chloro-2-{3-[3-(4-fluorobenzyl)-3,7,9-triazabicyclo[3.3.1]non-9-yl]-3-oxopropenyl}-phenyl)methanesulfonamide

1-(5-Chloro-2-{(E)-3-[3-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1]oct-8-yl]-3-oxopropenyl}-4-methoxyphenyl)-3-methylurea

(5-Chloro-2-{(E)-3-[3-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1]oct-8-yl]-3-oxopropenyl}-4-methoxyphenyl)-3-urea

N-(5-Chloro-2-{(E)-3-[3-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1]oct-8-yl]-3-oxopropenyl}-4-methoxyphenyl)-acetamide

N-(5-Chloro-2-{(E)-3-[9-(4-fluorobenzyl)-3-oxa-7,9-diazabicyclo[3.3.1]non-7-yl]-3-oxopropenyl}-4-methoxyphenyl)-acetamide

N-(5-Chloro-2-{(E)-3-[7-(4-fluorobenzyl)-3-oxa-7,9-diazabicyclo[3.3.1]non-9-yl]-3-oxopropenyl}-4-methoxyphenyl)-acetamide

(5-Chloro-2-{(E)-3-[3-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1]oct-8-yl]-3-oxopropenyl}-4-trifluoromethoxyphenyl)-urea

(5-Chloro-2-{(E)-3-[3-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1]oct-8-yl]-3-oxopropenyl}-4-methylphenyl)-urea

6-(5-Chloro-4-fluoro-2-{(E)-3-[3-(4-fluoro-benzyl)-3,8-diaza-bicyclo[3.2.1]oct-8-yl]-3-oxo-propenyl}-phenyl)-4,6-diaza-spiro[2.4]heptane-5,7-dione

6-(5-Chloro-2-{(E)-3-[3-(4-fluoro-benzyl)-3,8-diaza-bicyclo[3.2.1]oct-8-yl]-3-oxo-ropenyl}-4-methoxy-phenyl)-4,6-diaza-spiro[2.4]heptane-5,7-dione

(R)-3-(5-Chloro-2-{(E)-3-[3-(4-fluoro-benzyl)-3,8-diaza-bicyclo[3.2.1]oct-8-yl]-3-oxo-ropenyl}-4-trifluoromethyl-phenyl)-5-methyl-imidazolidine-2,4-dione

(R)-3-(5-Chloro-2-{(E)-3-[3-(4-fluoro-benzyl)-3,8-diaza-bicyclo[3.2.1]oct-8-yl]-3-oxo-propenyl}-4-trifluoromethoxy-phenyl)-5-methyl-imidazolidine-2,4-dione

(R)-3-(5-Chloro-2-{(E)-3-[3-(4-fluoro-benzyl)-3,8-diaza-bicyclo[3.2.1]oct-8-yl]-3-oxo-propenyl}-4-methoxy-phenyl)-5-methyl-imidazolidine-2,4-dione

N-(Chloro-2-{(E)-3-[(1S,3R,5R)-3-(4-fluorophenylamino)-8-azabicyclo[3.2.1]oct-8-yl]-3-oxopropenyl}-4-methoxyphenyl)-acetamide

or a pharmaceutically acceptable salt, or ester thereof.

The compounds of formula I and II and as listed above are herein after referred to as Agents of the Invention.

Pharmaceutically acceptable salts of the acidic Agents of the Invention are salts formed with bases, namely cationic salts such as alkali and alkaline earth metal salts, such as sodium, lithium, potassium, calcium, magnesium, as well as ammonium salts, such as ammonium, trimethyl-ammonium, diethylammonium, and tris-(hydroxymethyl)-methylammonium salts.

Similarly acid addition salts, such as of mineral acids, organic carboxylic and organic sulfonic acids e.g. hydrochloric acid, methanesulfonic acid, maleic acid, are also possible provided a basic group, such as pyridyl, piperazinyl, piperidinyl constitutes part of the structure.

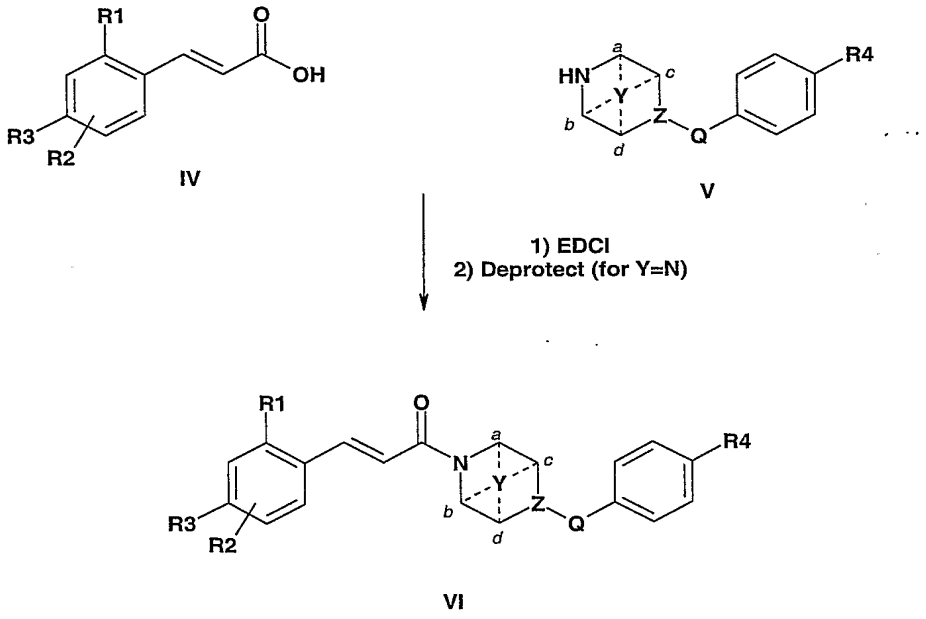
Agents of the Invention may also exist in the form of optical isomers; for example as hereinafter described in the Examples. Thus the invention includes both individual isomeric forms as well as mixtures, e.g. racemic and diastereoisomeric mixtures thereof, unless otherwise specified. Conveniently the invention includes compounds of formula I in purified isomeric form, e.g. comprising at least 90%, or preferably at least 95%, of a single isomeric form.

Where Agents of the Invention exist in isomeric form as aforesaid, individual isomers may be obtained in conventional manner, e.g. employing optically active starting materials or by separation of initially obtained mixtures, for example using conventional chromatographic techniques.

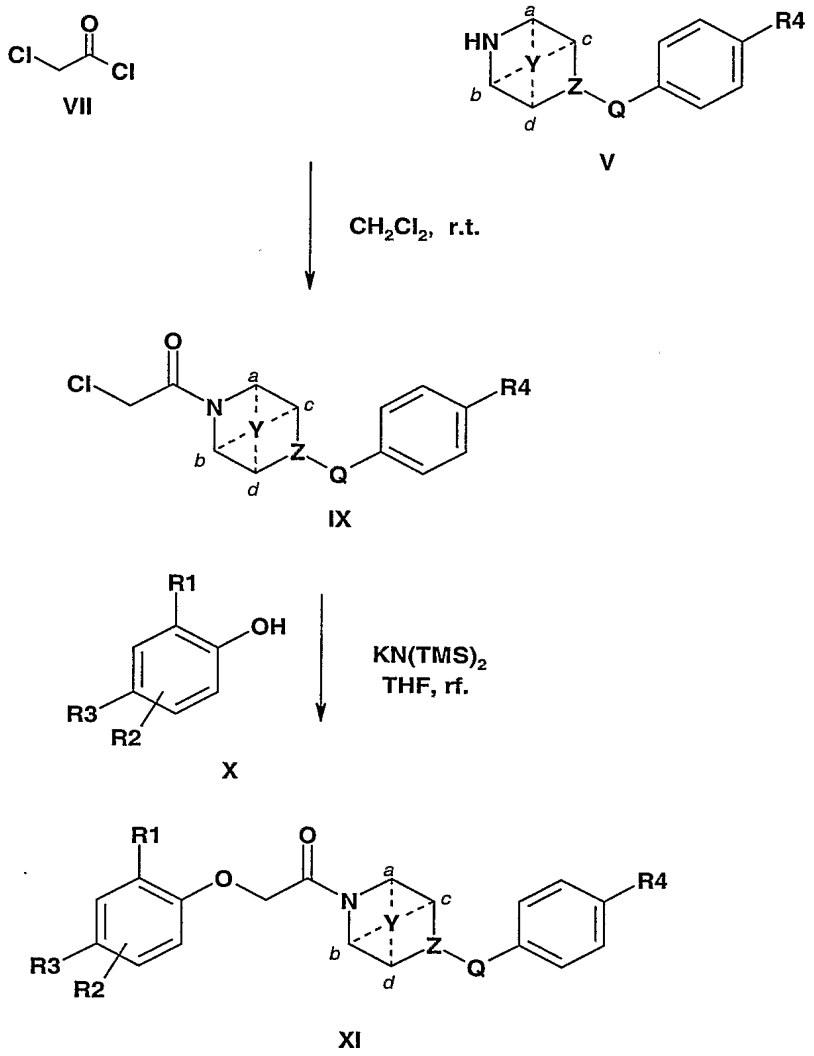
The Agents of the Invention which comprise free hydroxyl groups may also exist in the form of pharmaceutically acceptable, physiologically cleavable esters, and as such are included within the scope of the invention. Such pharmaceutically acceptable esters are preferably prodrug ester derivatives, such being convertible by solvolysis or cleavage under physiological conditions to the corresponding Agents of the Invention which comprise free hydroxyl groups. Suitable pharmaceutically acceptable prodrug esters are those derived from a carboxylic acid, a carbonic acid monoester or a carbamic acid, advantageously esters derived from an optionally substituted lower alkanoic acid or an arylcarboxylic acid.

Agents of the Invention may for example be prepared by processes as described below:

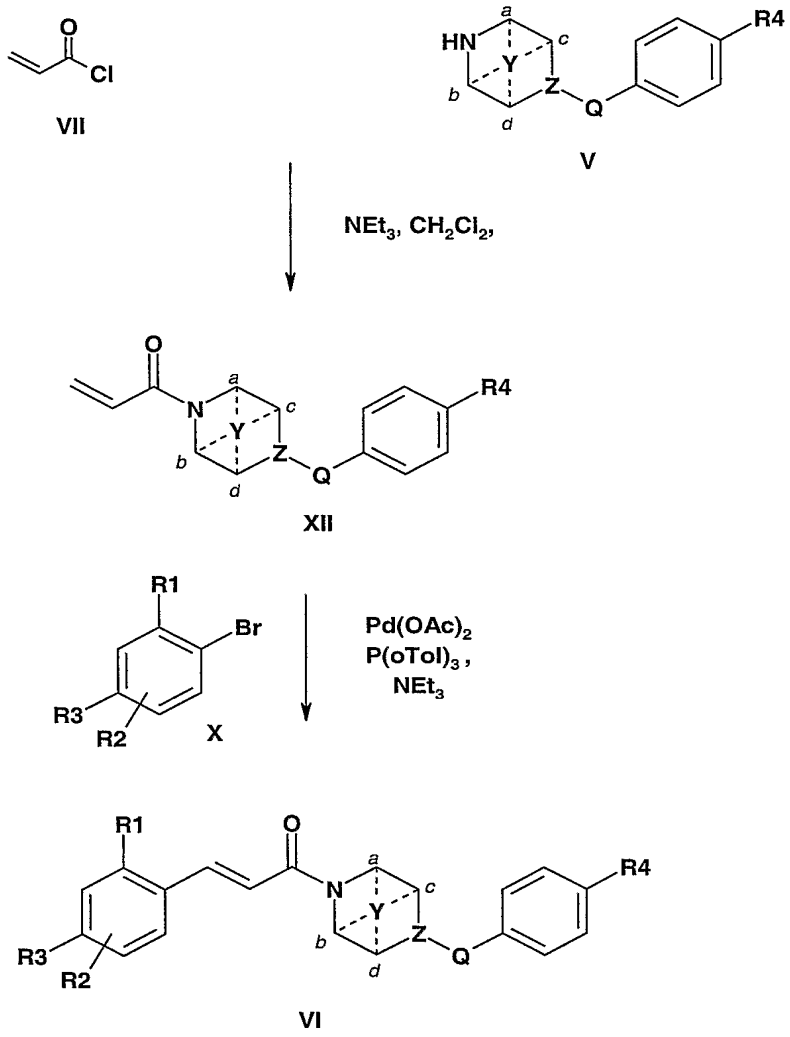
1) By condensing a compound of formula IV with a compound of formula V in the presence of a suitable agent, e.g. EDCI, followed by deprotection to give the desired compound VI:



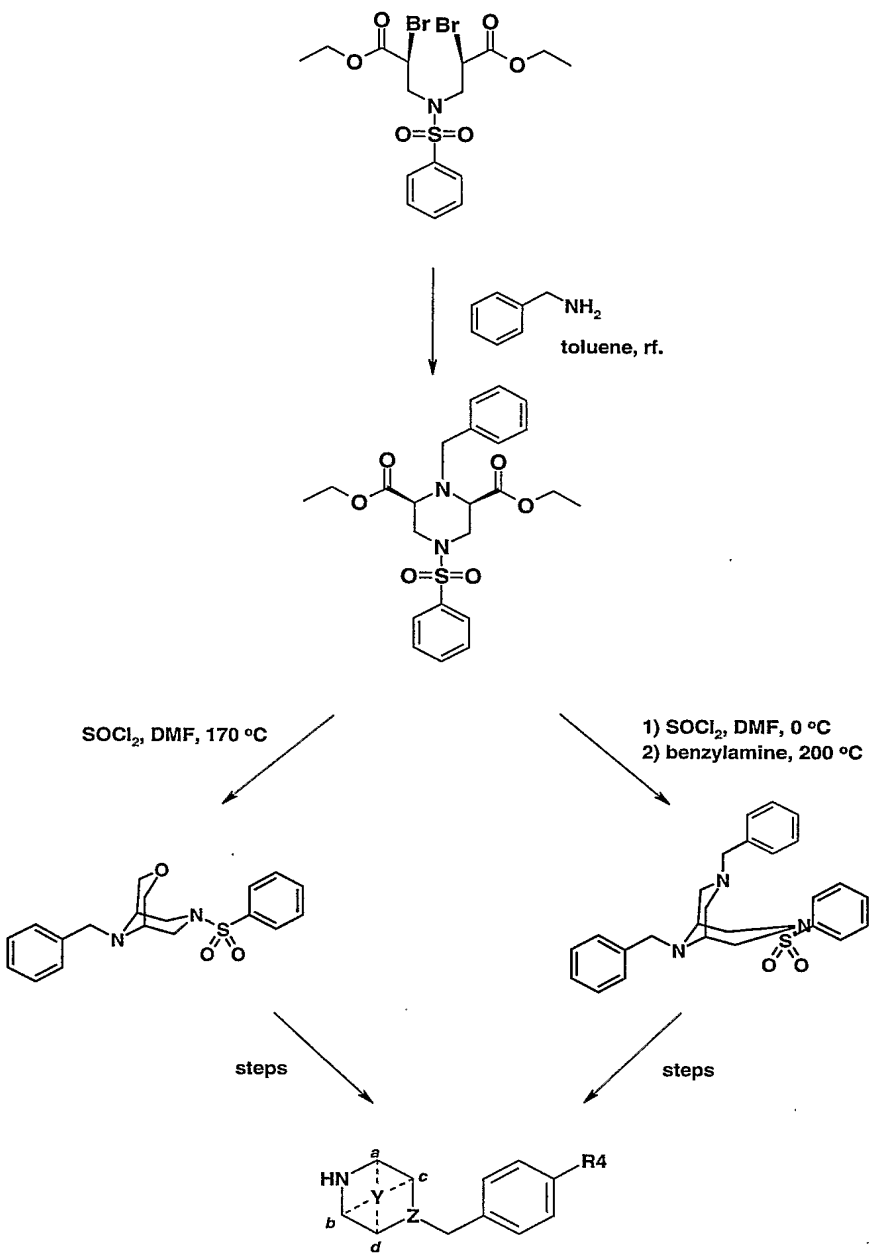
2) By reacting a compound of formula X with a compound of formula IX in the presence of a suitable reagent such as $KN(TMS)_2$, wherein the compound of formula IX is prepared by reacting a compound of formula VII with a compound of formula V as shown below:



3) By reacting a compound of formula X with a compound of formula XII in the presence of a suitable reagent such as palladium acetate, triarylphosphine and a base such as triethylamine, wherein the compound of formula XII may be prepared by reaction between a compound of formula VII and a compound of formula V in the presence of a base such as triethylamine:



4) The compounds of formula V (Y= $-CH_2OCH_2$, $-CH_2NRCH_2$-) may themselves be prepared by the following synthesis:



Compounds of formula V wherein Y is $-(CH_2)_n-$ may be synthesized by known methods.

EXPERIMENTAL SECTION

Abbreviations:

Ac_2O: Acetic anhydride

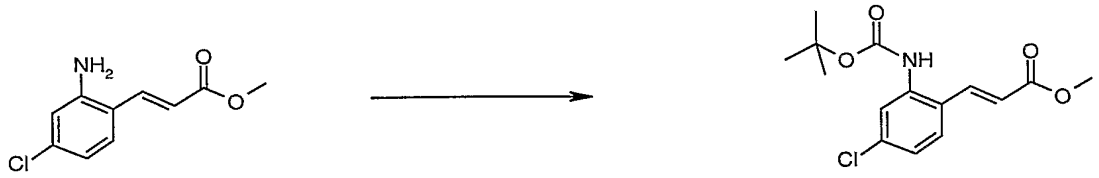
BOC:	tert.-Butyloxycarbonyl
DCC:	Dicyclohexyl-carbodiimide
DCM:	Dichloromethane
DMAP:	Dimethyl-pyridin-4-yl-amine
DME:	1,2-Dimethoxyethane
DMF:	N,N-Dimethyl formamide
EDCI:	(3-Dimethylamino-propyl)-ethyl-carbodiimide hydrochloride
HCl:	Hydrochloric acid
HOBT:	Benzotriazol-1-ol
NaOH:	Sodium hydroxide
NEt_3:	Triethylamine
TBME	tert.-Butyl-methylether
TFA:	Trifluoro-acetic acid
THF:	Tetrahydrofuran

Examples:

The following examples are for illustrative purposes only and are not intended to limit in any way the scope of the claimed invention:

Example 1: (E)-N-(5-Chloro-2-{3-[3-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1]oct-8-yl]-3-oxopropenyl}-phenyl)acetamide

(E)-3-(2-tert-Butoxycarbonylamino-4-chlorophenyl)-acrylic acid methyl ester (GR 1686)



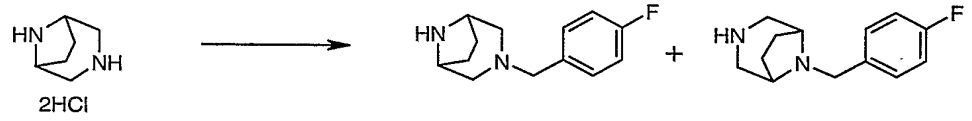
(E)-3-(2-Amino-4-chlorophenyl)-acrylic acid methyl ester (Carling, Robert W.; et al. J. Med. Chem. (1993), 36(22), 3397-408) (3.3 g, 15.6 mmol) in THF (63 ml) was combined with (BOC)2O (6.8 g, 31.2 mmol) and refluxed for 4 h. THF was evaporated and a second portion of (BOC)2O added (6.8g, 31.2 mmol). The mixture was heated to 100°C for 18 h. Recrystallisation from TBME/hexanes rendered the title compound as colorless crystals (4.6 g; 94 %).

1H-NMR (400MHz; DMSO-d6): 1.46 (s, 9H); 3.72 (s, 3H); 6.58 (d, 1H); 7.25 (dd, 1H); 7.47 (d, 1H); 7.72 (d, 1H); 7.82 (d, 1H); 9.33 (bs, 1H, NH).
MS (m/z) EI: 311 (M+, 20); 238 (10); 255 (20); 180 (70); 152 (65).

(E)-3-(2-tert-Butoxycarbonylamino-4-chlorophenyl)-acrylic acid

(E)-3-(2-tert-Butoxycarbonylamino-4-chlorophenyl)-acrylic acid methyl ester (4.6 g, 14.7 mmol) was dissolved in MeOH (300 ml), 2N NaOH (11 ml, 22 mmol) and water (147 ml) added and stirred at 50°C for 1 h. The clear reaction mixture was concentrated to ~150ml, acidified to pH 3 and extracted twice with TBME. The combined organic phases were dried over Na2SO4 and evaporated to dryness to yield the title acid as colorless crystals (3.8 g, 87 %).

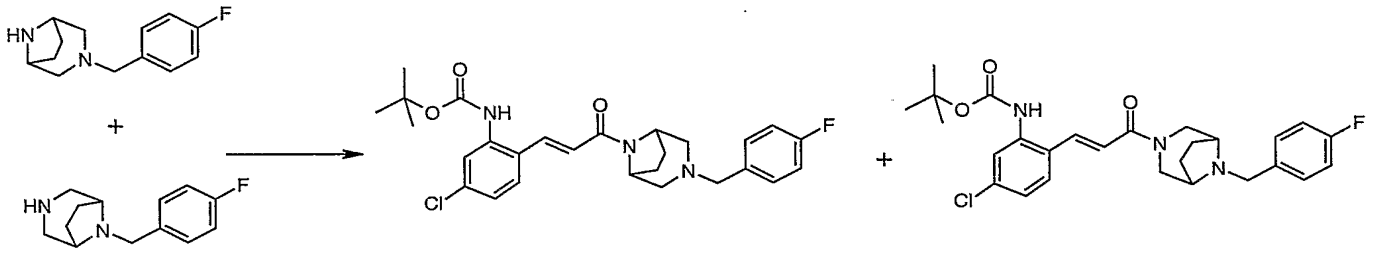
3-(4-Fluorobenzyl)-3,8-diazabicyclo[3.2.1]octane and 8-(4-Fluorobenzyl)-3,8-diazabicyclo[3.2.1]



3,8-Diazabicyclo[3.2.1]octane dihydrochloride (MicroChemistry Building Blocks, Moscow) (300 mg; 1.6 mmol), 4-fluorobenzylchloride (0.18 ml; 1.6 mmol) and NaHCO3 (685 mg; 8.1 mmol) were refluxed in EtOH (6 ml) for 2.5 h. TBME (15 ml) was added, the reaction mixture was filtered, evaporated to dryness and the residue purified by chromatography (SiO2,

TBME/MeOH/NH3conc 90/15/2) to yield an inseparable mixture of the title compounds as light yellow oil (160mg; 46%), which was used in the next step.

(E)-(5-Chloro-2-{3-[3-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1]oct-8-yl-3-oxopropenyl}phenyl)-carbamic acid tert-butyl ester (A; BL 5334-II) and (E)-(5-Chloro-2-{3-[8-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1]oct-3-yl-3-oxopropenyl}phenyl)-carbamic acid tert-butyl ester



The mixture of 3-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1]octane and 8-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1] from the previous reaction (240 mg; 1.1 mmol), (E)-3-(2-tert-butoxycarbonyl amino-4-chlorophenyl)-acrylic acid (324 mg; 1.1 mmol) and EDCI.HCl (210 mg; 1.1 mmol) were dissolved in CH2Cl2 (6 ml) and stirred at room temperature for 18 h. The reaction mixture was purified via chromatography (SiO2; acetone/hexanes 15/85) to yield B (98 mg; 18 %; colorless foam), which was eluted first, followed by A (371mg; 68%) as colorless crystals.

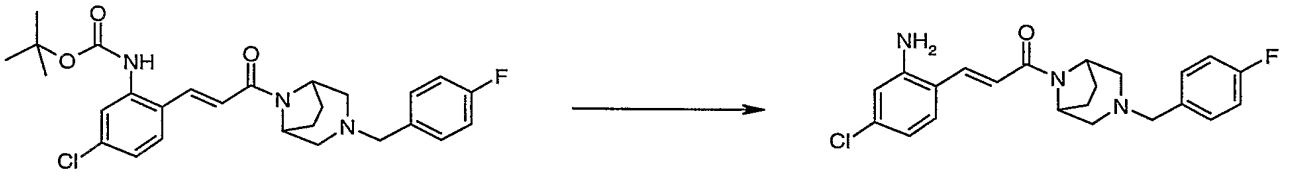
Compound A. 1H-NMR (400MHz; DMSO-d6), δ (ppm): 1.47 (s, 9H); 1.67-2.05 (m, 4H); 2.18 (dd, 2H); 2.68 (dd, 2H); 3.46 (s, 2H); 4.55 (d, 1H); 4.68 (bd, 1H); 7.06 (d, 1H); 7.16 (t, 2H); 7.25 (dd, 1H); 7.35 (dd, 2H); 7.46 (s, 1H); 7.66 (d, 1H); 7.89 (d, 1H); 9.23 (s, 1H).

MS (m/z) ES+: 500.2 (MH+, 100).

Compound B. 1H-NMR (400MHz; DMSO-d6), δ (ppm): 0.81-0.91 (m, 1H); 1.48 (s, 9H); 1.53-1.62 (m, 1H); 1.95 (bs, 2H); 2.83 (d, 1H); 3.18 (bs, 2H); 3.28 (d, 1H); 3.51 (d, 2H); 3.96 (d, 1H); 4.13 (d, 1H); 7.11 (d, 1H); 7.16 (t, 2H); 7.25 (dd, 1H); 7.41-7.46 (m, 3H); 7.63 (d, 1H); 7.87 (d, 1H); 9.23 (s, 1H).

MS (m/z) ES+: 500.2 (MH+, 100).

(E)-3-(2-Amino-4-chlorophenyl)-1-[3-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1]oct-8-yl]-propenone

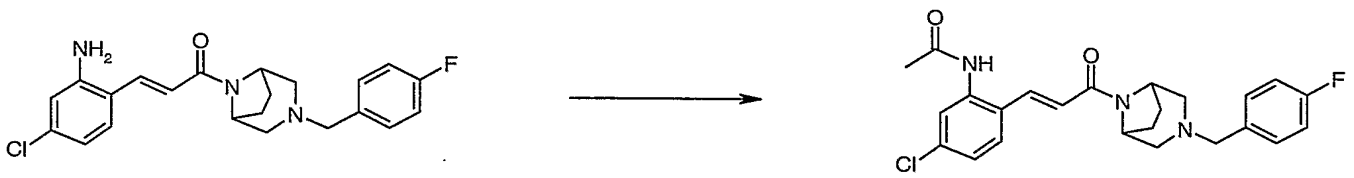


(E)-(5-Chloro-2-{3-[3-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1]oct-8-yl-3-oxopropenyl}phenyl)-carbamic acid tert-butyl ester (A from the reaction above; 365 mg; 0.7 mmol) was dissolved in EtOH/HClconc. (4 ml /4 ml) and stirred for 2 min., poured on a saturated solution of Na2CO3 and extracted with TBME three times. The combined organic phases were dried over Na2SO4 and evaporated to dryness to yield the title compound as yellow foam (292 mg; 100 %).

1H-NMR (400MHz; DMSO-d6), δ (ppm): 1.68-1.97 (m, 4H); 2.18 (dd, 2H); 2.67 (dd, 2H); 3.48 (s, 2H); 4.55 (d, 1H); 4.63 (bd, 1H); 5.75 (s, 2H, NH2); 6.54 (dd, 1H); 6.73 (d, 1H); 6.89 (d, 1H); 7.17 (t, 2H); 7.35 (dd, 2H); 7.55 (d, 1H); 7.68 (d, 1H).

MS (m/z) ES+: 400.2 (MH+, 100).

(E)-N-(5-Chloro-2-{3-[3-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1]oct-8-yl]-3-oxopropenyl}-phenyl)acetamide



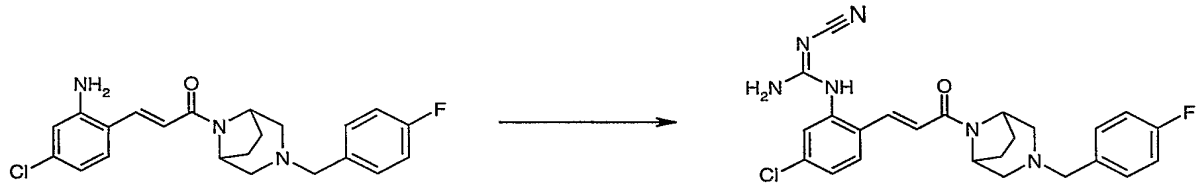
(E)-3-(2-Amino-4-chlorophenyl)-1-[3-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1]oct-8-yl]-propenone (50 mg; 0.12 mmol) and NEt3 (0.17 ml; 1.2 mmol) were dissolved in THF (4 ml) and treated with acetyl chloride (0.088 ml; 1.2 mmol). The reaction mixture was refluxed for 2 min. and kept at room temperature for 10 min., poured on a saturated solution of Na2CO3 and extracted with TBME three times. The combined organic phases were dried over

Na2SO4 and evaporated to dryness. Purification via chromatography (SiO2; TBME/MeOH/NH3conc 97/3/0.3) delivered the title compound as colorless crystals (31 mg; 56 %).

1H-NMR (400MHz; DMSO-d6), δ (ppm): 1.68-1.79 (m, 1H); 1.82-1.97 (m, 3H); 2.09 (s, 3H); 2.15 (dd, 2H); 2.68 (bt, 2H); 3.47 (s, 2H); 4.55 (d, 1H); 4.70 (s, 1H); 7.11 (d, 1H); 7.17 (t, 2H); 7.30 (dd, 1H); 7.36 (dd, 2H); 7.59 (d, 1H); 7.68 (d, 1H); 7.93 (d, 1H); 9.93(s, 1H).

MS (m/z) ES+: 442.2 (MH+, 50).

Example 2: (E)-N-(5-Chloro-2-{3-[3-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1]oct-8-yl]-3-oxopropenyl}-phenyl)-N'-cyanoguanidine



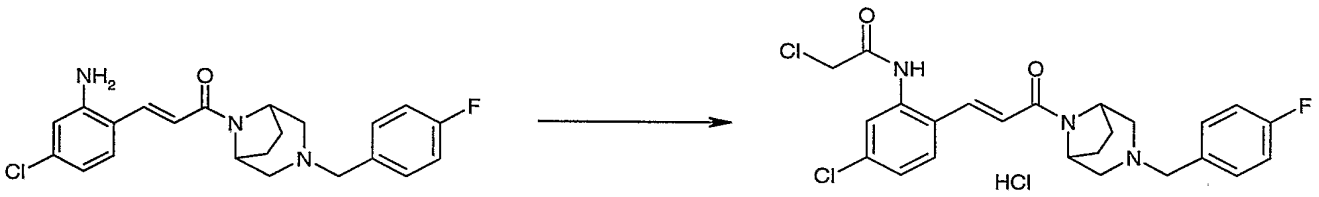
(E)-3-(2-Amino-4-chlorophenyl)-1-[3-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1]oct-8-yl]-propenone (100 mg; 0.25 mmol) was suspended in ethoxyethanol/water (4 ml/2 ml). The reaction mixture was heated to reflux and treated with NaN(CN)2 (89 mg; 1 mmol) followed by 2N HCl (0.5 ml; 1 mmol). After 5 min. at reflux a second portion of NaN(CN)2 (178 mg; 2 mmol) followed by 2 N HCl (1 ml; 2 mmol) was added and refluxed for 5 min. The reaction mixture was poured on a saturated solution of Na2CO3 and extracted with TBME three times. The combined organic phases were dried over Na2SO4, evaporated to dryness and purified via preparative HPLC (XTerra, RP18, 7µm, acetonitrile/water) to deliver the title compound as colorless crystals (12 mg; 10 %).

1H-NMR (400MHz; DMSO-d6), δ (ppm): 1.71-1.98 (m, 4H); 2.18 (dd, 2H); 2.68 (dd, 2H); 3.48 (s, 2H); 4.55 (d, 1H); 4.70 (bs, 1H); 7.09-7.22 (m, 4H); 7.30-7.38 (m, 3H); 7.43 (d, 1H); 7.58 (d, 1H); 7.93 (d, 1H); 9.13 (bs, 1H).

MS (m/z) ES+: 467.1 (MH+, 100).

Example 3: (E)-N-(5-Chloro-2-{3-[3-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1]oct-8-yl]-3-oxopropenyl}-phenyl)-2-dimethylaminoacetamide

(E)-2-Chloro-N-(5-chloro-2-{3-[3-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1]oct-8-yl]-3-oxopropenyl}-phenyl)acetamide hydrochloride

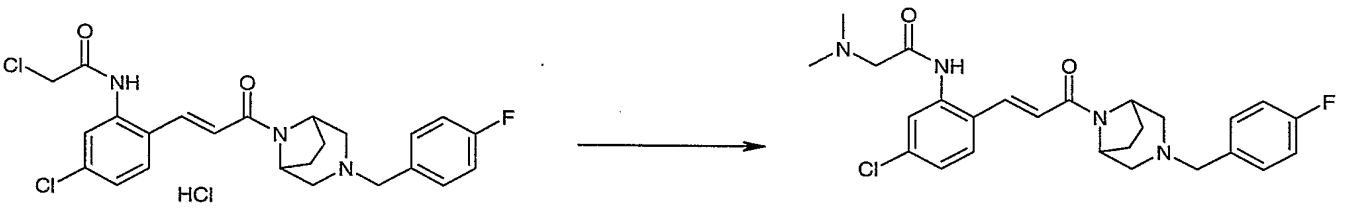


(E)-3-(2-Amino-4-chlorophenyl)-1-[3-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1]oct-8-yl]-propenone (50 mg; 0.12 mmol) was dissolved in THF (1 ml) and treated with chloroacetylchloride (0.011 ml; 0.14 mmol) and stirred at room temperature for 1 h. TBME was added to the reaction mixture, the white precipitate filtered, washed and dried to yield the desired product (55 mg; 85 %).

1H-NMR (400MHz; DMSO-d6), δ (ppm): 1.83-2.24 (m, 4H); 3.10-3.35 (m, 4H); 4.33 (bs, 2H); 4.36 (s, 2H); 4.76 (bs, 1H); 4.94 (bs, 1H); 7.18 (d, 1H); 7.30 (bt, 2H); 7.40 (bd, 1H); 7.55 (d, 1H); 7.68-7.78 (m, 3H); 7.94 (d, 1H); 10.30 (bs, 2H).

MS (m/z) ES+: 476.1 (MH+, 100).

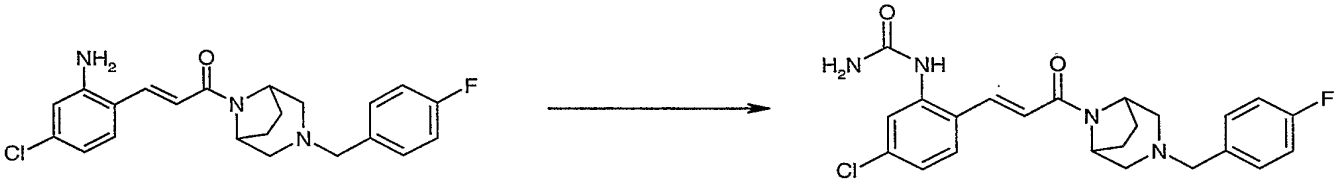
(E)-N-(5-Chloro-2-{3-[3-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1]oct-8-yl]-3-oxopropenyl}-phenyl)-2-dimethylaminoacetamide



(E)-2-Chloro-N-(5-chloro-2-{3-[3-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1]oct-8-yl]-3-oxopropenyl}-phenyl)acetamide hydrochloride (50 mg; 0.1 mmol) was suspended in THF (2 ml) and treated with an excess of dimethylamine (~0.5 ml). The reaction mixture was poured

on a silica gel column and purified (TBME/MeOH/NH3conc 95/5/0.5) to give the title compound as a colorless foam (48 mg; 95 %).
1H-NMR (400MHz; DMSO-d6), δ (ppm): 1.68-1.98 (m, 4H); 2.18 (dd, 2H); 2.33 (s, 6H); 3.18 (dd, 2H); 3.12 (s, 2H); 3.48 (d, 2H); 4.55 (d, 1H); 4.70 (bs, 1H); 7.10 (d, 1H); 7.16 (t, 2H); 7.30 (dd, 1H); 7.36 (dd, 2H); 7.61 (d, 1H); 7.65 (d, 1H); 7.92 (d, 1H); 9.83 (s, 1H).
MS (m/z) ES+: 485.2 (MH+, 100).

Example 4: (E)-(5-Chloro-2-{3-[3-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1]oct-8-yl]-3-oxopropenyl}-phenyl)-urea



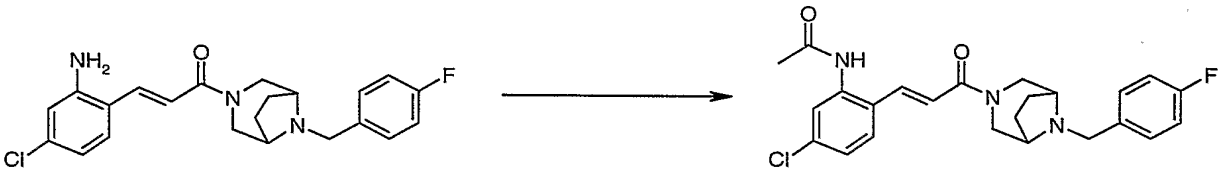
(E)-3-(2-Amino-4-chlorophenyl)-1-[3-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1]oct-8-yl]-propenone (50 mg; 0.12 mmol) was dissolved in HOAc (1 ml). Water (2 ml) was added, followed by NaOCN (100 mg; 1.5 mmol). The reaction mixture was kept at room temperature for 20 min., then poured on a saturated solution of Na2CO3. The white precipitate was filtered and purified further by chromatography (SiO2; acetone/hexanes 6/4 to 8/2) to render the target compound as colorless crystals
22 mg; 40 %).
1H-NMR (400MHz; DMSO-d6), δ (ppm): 1.58-1.98 (m, 4H); 2.17 (dd, 2H); 2.68 (dd, 2H); 3.46 (s, 2H); 4.56 (d, 1H); 4.69 (bs, 1H); 6.25 (s, 2H, NH2); 7.04 (d, 1H); 7.05 (d, 1H); 7.15(t, 2H); 7.35 (dd, 2H); 7.70 (d, 1H); 7.78 (d, 1H); 7.96 (d, 1H); 8.43 (s, 1H, NH).
MS (m/z) ES+: 443.2 (MH+, 100).

Example 5: (E)-N-(5-Chloro-2-{3-[8-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1]oct-3-yl]-3-oxopropenyl}-phenyl)acetamide

(E)-3-(2-Amino-4-chlorophenyl)-1-[8-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1]oct-3-yl]-propenone

(E)-(5-Chloro-2-{3-[8-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1]oct-3-yl-3-oxopropenyl}phenyl)-carbamic acid tert-butyl ester (95 mg; 0.19 mmol) was dissolved in EtOH/HClconc (2 ml/2 ml), kept 2 min. at room temp., poured on a saturated solution of Na2CO3 and extracted with TBME three times. The combined organic phases were dried over Na2SO4, evaporated to dryness and yielded the title compound as a yellow foam (77 mg; 97%).
1H-NMR (400MHz; DMSO-d6), δ (ppm): 1.43-1.61 (m, 2H); 1.95 (bs, 2H); 2.83 (d, 1H); 3.16 (bs, 2H); 3.26 (d, 1H); 3.50 (s, 2H); 3.92 (d, 1H); 4.15 (d, 1H); 5.74 (s, 2H, NH2); 6.54 (dd, 1H); 6.73 (d, 1H); 6.93 (d, 1H); 7.17 (t, 2H); 7.43 (dd, 2H); 7.52 (d, 1H); 7.63 (d, 1H).
MS (m/z) ES+: 400.2 (MH+, 100).

(E)-N-(5-Chloro-2-{3-[8-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1]oct-3-yl]-3-oxopropenyl}-phenyl)acetamide

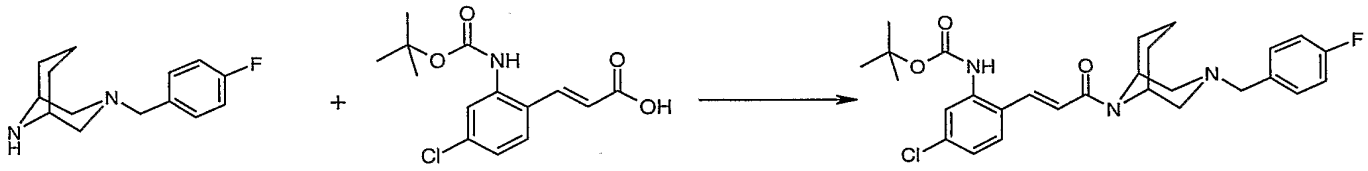


(E)-3-(2-Amino-4-chlorophenyl)-1-[8-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1]oct-3-yl]-propenone (37 mg; 0.075 mmol) was dissolved in THF (2 ml) and NEt3 (0.1 ml; 0.75 mmol). Acetylchloride (0.052 ml; 0.75 mmol) was added and the reaction mixture refluxed for 5 min., poured on a saturated solution of Na2CO3 and extracted with TBME three times. The combined organic phases were dried over Na2SO4, evaporated to dryness and purified via chromatography (SiO2, acetone/hexanes 4/6) to yield the title compound as colorless foam (23 mg; 71 %).

1H-NMR (400MHz; DMSO-d6), δ (ppm): 1.46 (bt, 1H); 1.58 (bt, 1H); 1.96 (bs, 2H); 2.10 (s, 3H); 2.85 (d, 1H); 3.18 (bs, 2H); 3.28 (d, 1H); 3.51 (d, 2H); 3.97 (d, 1H); 4.13 (d, 1H); 7.15 (d, 1H); 7.16(t, 2H); 7.28 (dd, 1H); 7.45 (dd, 2H); 7.58(d, 1H); 7.63 (d, 1H); 7.91(d, 1H); 9.91 (s, 1H).
MS (m/z) ES+: 442.2 (MH+, 100).

Example 6: (E)-N-(5-Chloro-2-{3-[3-(4-fluorobenzyl)-3,9-diazabicyclo[3.3.1]non-9-yl]-3-oxopropenyl}-phenyl)-acetamide

(E)-(5-Chloro-2-{3-[3-(4-fluorobenzyl)-3,9-diazabicyclo[3.3.1]non-9-yl]-3-oxopropenyl}-phenyl)-carbamic acid tert-butyl ester



3-(4-Fluorobenzyl)-3,9-diazabicyclo[3.3.1]nonane (Blumberg, L.C. et al., WO 0232901) (394 mg; 1.5 mmol) and (E)-3-(2-tert-butoxycarbonylamino-4-chlorophenyl)-acrylic acid (450 mg; 1.5 mmol) were dissolved in CH2Cl2 (15 ml) and treated with EDCI.HCl (288 mg; 1.5 mmol) for 12 h. The reaction mixture was poured on a column of SiO2 and chromatographed (TBME/MeOH/NH3conc 95/4.5/0.5 to 90/9/1) to give the desired product as a colorless foam (450 mg; 58 %).
1H-NMR (400MHz; DMSO-d6), δ (ppm): 1.48 (s, 9H); 1.50-1.60 (m, 2H); 1.67-1.80 (m, 4H); 2.19 (d, 1H); 2.29 (d, 1H); 2.82-2.95 (m, 2H); 3.40 (d, 2H); 4.47 (bs, 1H); 4.60 (bs, 1H); 7.11-7.27(m, 4H); 7.33-7.39(m, 2H); 7.47 (s, 1H); 7.67 (d, 1H); 7.89(d, 1H); 9.22 (s, 1H).
MS (m/z) ES+: 514.2 (MH+, 100).

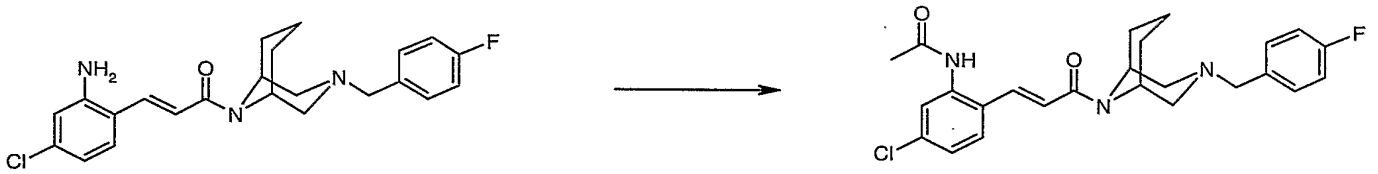
(E)-3-(2-Amino-4-chlorophenyl)-1-[3-(4-fluorobenzyl)-3,9-diaza-bicyclo[3.3.1]non-9-yl]-propenone

(E)-(5-Chloro-2-{3-[3-(4-fluorobenzyl)-3,9-diazabicyclo[3.3.1]non-9-yl]-3-oxopropenyl}-phenyl)-carbamic acid tert-butyl ester (450 mg; 0.875 mmol) was dissolved in EtOH/HClconc (3.5 ml /3.5 ml), kept at room temp. for 1 h, poured on a column of SiO2 and chromatographed (TBME/MeOH/NH3conc 95/4.5/0.1) to give the desired product as a yellow foam (350 mg; 95 %).

1H-NMR (400MHz; DMSO-d6), δ (ppm): 1.50-1.58 (m, 1H); 1.66-1.82 (m, 4H); 2.18(dd, 1H); 2.28(dd, 1H); 2.76-2.93(m, 3H); 3.40 (d, 2H); 4.42 (bs, 1H); 4.60(bs, 1H); 5.73 (s, 2H); 6.53(d, 1H); 6.73 (d, 1H); 6.96(d, 1H); 7.19(t, 2H); 7.36(dd, 2H); 7.53(d, 1H); 7.68(d, 1H).

MS (m/z) ES+: 414.2 (MH+, 100).

<u>(E)-N-(5-Chloro-2-{3-[3-(4-fluorobenzyl)-3,9-diazabicyclo[3.3.1]non-9-yl]-3-oxopropenyl}-phenyl)-acetamide</u>



(E)-3-(2-Amino-4-chlorophenyl)-1-[3-(4-fluorobenzyl)-3,9-diaza-bicyclo[3.3.1]non-9-yl]-propenone (62 mg; 0.15 mmol) (62 mg; 0.15 mmol) was treated as in Example 1 and purified via chromatography (SiO2; TBME/MeOH/NH3conc 98/1.8/0.2) to yield the title compound as a colorless foam (50 mg; 73 %).

1H-NMR (500MHz; DMSO-d6), δ (ppm): 1.53 (m, 1H); 1.60-1.80(m, 4H); 2.08 (s, 3H); 2.15(d, 1H); 2.25(d, 1H); 2.80-2.93(m, 3H); 3.42(d, 2H); 4.48(s, 1H); 4.58(s, 1H); 7.17(m, 3H); 7.25(d, 1H); 7.32(d, 2H); 7.55(s, 1H); 7.65(d, 1H); 7.92(d, 1H); 9.93(s, 1H).

MS (m/z) ES+: 478.1 (MH+, 100).

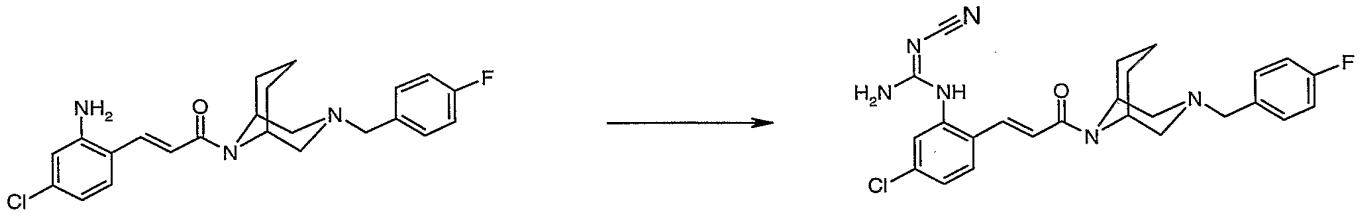
Example 7: (E)-N-(5-Chloro-2-{3-[3-(4-fluorobenzyl)-3,9-diazabicyclo[3.3.1]non-9-yl]-3-oxopropenyl}-phenyl)-urea

3-(2-Amino-4-chlorophenyl)-1-[3-(4-fluorobenzyl)-3,9-diazabicyclo[3.3.1]non-9-yl]-propenone (62 mg; 0.15 mmol) was treated as in Example 4 and purified by chromatography (SiO2; TBME/MeOH/NH3conc 98/1.8/0.2) to render the target compound as colorless foam (50 mg; 72 %).

1H-NMR (500MHz; DMSO-d6), δ (ppm): 1.51 (m, 1H); 1.60-1.81(m, 4H); 2.15(dd, 1H); 2.25(d, 1H); 2.75-2.92(m, 3H); 3.40(d, 2H); 4.47(s, 1H); 4.58(s, 1H); 6.30(s, 2H, NH2); 7.05 (d, 1H); 7.18(m, 3H); 7.32(m, 2H); 7.69(d, 1H); 7.78(d, 1H); 7.98(s, 1H); 8.41(s, 1H, NH).

MS (m/z) ES+: 457.1 (MH+, 100).

Example 8: (E)-N-(5-Chloro-2-{3-[3-(4-fluorobenzyl)-3,9-diazabicyclo[3.3.1]non-9-yl]-3-oxopropenyl}-phenyl)-N'-cyanoguanidine

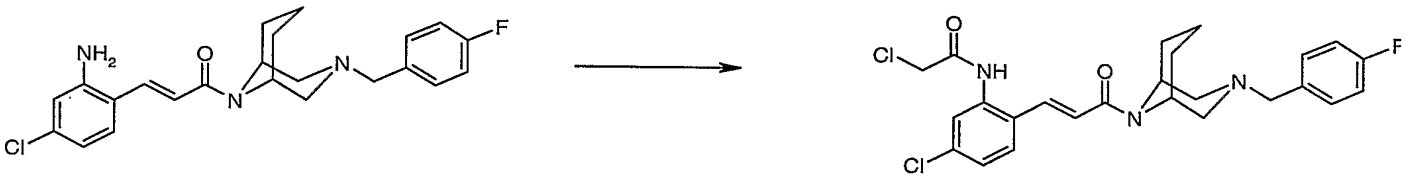


(E)-3-(2-Amino-4-chlorophenyl)-1-[3-(4-fluorobenzyl)-3,9-diazabicyclo[3.3.1]non-9-yl]-propenone (62 mg; 0.15 mmol) was treated as in Example 2 and purified by chromatography (SiO2; TBME/MeOH/NH3conc 98/1.8/0.2) to yield the target compound as colorless crystals (35 mg; 36 %).

1H-NMR (500MHz; DMSO-d6), δ (ppm): 1.51(m, 1H); 1.61-1.81(m, 4H); 2.15(d, 1H); 2.25(d, 1H); 2.75-2.94(m, 3H); 3.40(d, 2H); 4.48(s, 1H); 4.59(s, 1H); 7.20(t, 2H); 7.23(d, 1H); 7.30(d, 3H); 7.40(s, 1H); 7.50(d, 1H); 7.92(d, 1H); 9.02 (s, 1H).
MS (m/z) ES+: 481.2 (MH+, 100).

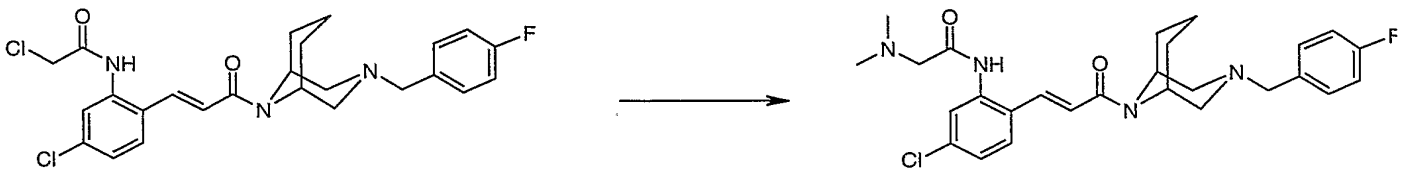
Example 9: (E)-N-(5-Chloro-2-{3-[3-(4-fluorobenzyl)-3,9-diazabicyclo[3.3.1]non-9-yl]-3-oxopropenyl}-phenyl)-2-dimethylaminoacetamide

(E)-2-Chloro-N-(5-chloro-2-{3-[3-(4-fluorobenzyl)-3,9-diazabicyclo[3.3.1]non-9-yl]-3-oxopropenyl}-phenyl)-acetamide



(E)-3-(2-Amino-4-chlorophenyl)-1-[3-(4-fluorobenzyl)-3,9-diaza-bicyclo[3.3.1]non-9-yl]-propenone (83 mg; 0.2 mmol) was dissolved in THF (4 ml) and NEt3 (0.034 ml; 0.48 mmol) and treated with chloroacetylchloride (0.019 ml; 0.24 mmol) at room temp. for 1 h. The reaction mixture was poured on a saturated solution of Na2CO3 and extracted with EtOAc three times. The combined organic phases were dried over Na2SO4, evaporated to dryness and purified via chromatography (SiO2, TBME/hexanes 6/4) to yield the tile compound as colorless foam (80 mg; 81 %).
1H-NMR (400MHz; DMSO-d6), δ (ppm): 1.51-1.59(m, 1H); 1.67-1.85(m, 4H); 2.18(bd, 1H); 2.28(bd, 1H); 2.78-2.95(m, 3H); 3.40(dd, 2H); 4.35(s, 2H); 4.46(bs, 1H); 4.58(bs, 1H); 7.18(t, 2H); 7.24(d, 1H); 7.42-7.49(m, 3H); 7.60(d, 1H); 7.65(d, 1H); 7.96(d, 1H); 10.23(s, 1H).
MS (m/z) ES+: 490.1 (MH+, 100).

(E)-N-(5-Chloro-2-{3-[3-(4-fluorobenzyl)-3,9-diazabicyclo[3.3.1]non-9-yl]-3-oxopropenyl}-phenyl)-2-dimethylaminoacetamide



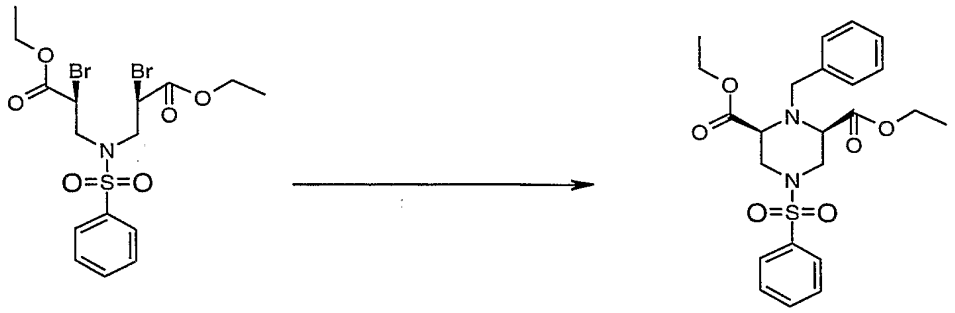
(E)-2-Chloro-N-(5-chloro-2-{3-[3-(4-fluorobenzyl)-3,9-diazabicyclo[3.3.1]non-9-yl]-3-oxopropenyl}-phenyl)-acetamide (80 mg; 0.16 mmol) was treated with dimethylamine in THF as in Example 3. The product was purified by via chromatography (SiO2, TBME/MeOH/NH3conc, 97/2.7/0.3) to yield the title compound as colorless foam (60 mg; 75 %).

1H-NMR (400MHz; DMSO-d6), δ (ppm): 1.51-1.61(m, 1H); 1.67-1.86(m, 4H); 2.19(bd, 1H); 2.28(bd, 1H); 2.35(s, 6H); 2.80-2.96(m, 3H); 3.33(s, 2H); 3.41(dd, 2H); 4.48(bs, 1H); 4.61(bs, 1H); 7.15-7.23(m, 3H); 7.30(d, 1H); 7.37(dd, 2H); 7.60(d, 1H); 7.65(s, 1H); 7.93(d, 1H); 9.82 (s, 1H).

MS (m/z) ES+: 499.1 (MH+, 100).

Example 10: N-(5-Chloro-2-{2-[7-(4-fluorobenzyl)-3-oxa-7,9-diazabicyclo[3.3.1]non-9-yl]-2-oxoethoxy}-phenyl)acetamide

(meso)-4-Benzenesulfonyl-1-benzylpiperazine-2,6-dicarboxylic acid diethyl ester



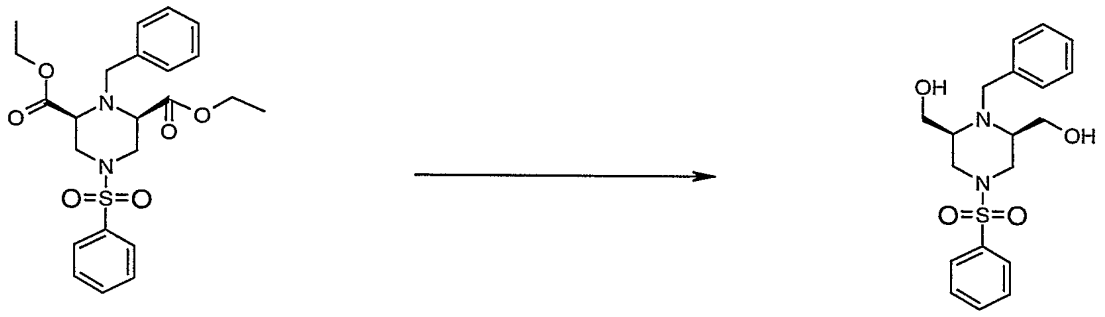
(meso)-3-[Benzenesulfonyl-(2-bromo-2-ethoxycarbonylethyl)-amino]-2-bromopropionic acid ethyl ester (Terauchi Hiromi et al., Chem. Pharm. Bull. (1975), 23(12), 3162-9) (8 g; 15.5 mmol) and benzylamine (5.1 ml; 46.6 mmol) were heated in toluene (30 ml) at 90^0 C for 1.5 h. The precipitated benzylamine.HBr was filtered, the filtrate evaporated to dryness and

purified via chromatography (TBME/hexanes 3/7) to yield the title compound as colorless crystals (4.35 g; 61 %).

1H-NMR (400MHz; DMSO-d6), δ (ppm): 1.17(t, 6H); 2.86(dd, 2H); 3.35(dd, 2H); 3.48(dd, 2H); 3.97(s, 2H); 4.00(q, 4H); 7.20-7.30(m, 5H); 7.63-7.80(m, 5H).

MS (m/z) ES+: 461.2 (MH+, 30).

(meso)-(4-Benzenesulfonyl-1-benzyl-6-hydroxymethyl-piperazin-2-yl)-methanol

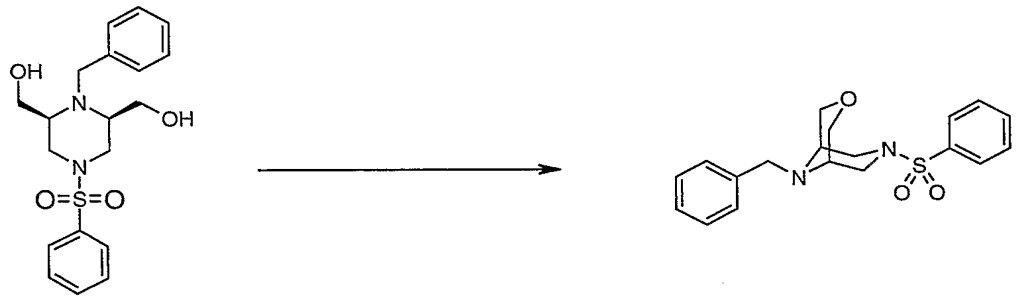


A 1M solution of LiAlH4 in THF (28 ml; 28 mmol) was added dropwise under cooling and stirring to *(meso)*-4-benzenesulfonyl-1-benzylpiperazine-2,6-dicarboxylic acid diethyl ester (4.34 g; 9.4 mmol) in THF (110 ml). After completed LiAlH4 addition, the reaction mixture was refluxed for 20 min., poured on a saturated solution of Na2CO3 and extracted with TBME three times. The combined organic phases were dried over Na2SO4 and evaporated to dryness to yield a colorless solid, which was washed with TBME to yield the title compound as white crystals (2.88 g; 81 %).

1H-NMR (400MHz; DMSO-d6), δ (ppm): 2.48-2.58(m, 2H); 2.62-2.69(m, 2H); 3.05-3.2(m, 2H); 3.24-3.30(dd, 2H); 3.43-3.50(m, 2H); 3.80(s, 2H); 4.65(t, 2H); 7.20-7.35(m, 5H); 7.65-7.80(m, 5H).

MS (m/z) ES-: 375.3 (M-H, 100).

7-Benzenesulfonyl-9-benzyl-3-oxa-7,9-diazabicyclo[3.3.1]nonane



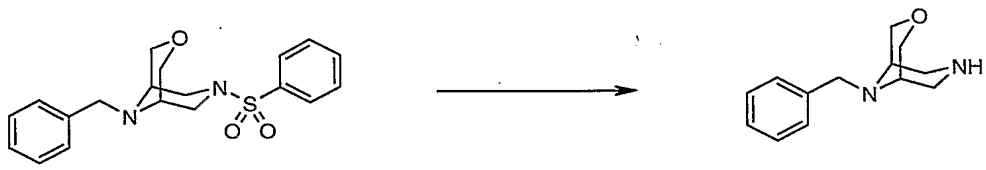
SOCl2 (0.97 ml; 13.4 mmol) in toluene (10 ml) was added under stirring at room temp. rapidly but dropwise to a solution of *(meso)*-(4-benzenesulfonyl-1-benzyl-6-hydroxymethylpiperazin-2-yl)-methanol (5.05 g; 13.4 mmol) in DMF (200 ml). The reaction mixture was heated in an oil bath (170°C) under reflux for 75 min. The reaction mixture was evaporated, taken up in a saturated solution of Na2CO3 and extracted with TBME three times. The combined organic phases were dried over Na2SO4, filtered, evaporated to dryness and purified via chromatography (SiO2, acetone/hexanes 1/9 to 3/7) to yield the title product as colorless crystals (2.1 g; 43 %).

1H-NMR (400MHz; DMSO-d6), δ (ppm): 2.65(bs, 2H); 2.83(bd, 2H); 3.49(d, 2H); 3.68(s, 2H); 3.70(d, 2H); 3.88(d, 2H); 7.20(m, 2H); 7.28(m, 3H); 7.68(m, 2H); 7.75(m, 3H).

COSY and HSQC spectra are in agreement with the structure.

MS (m/z) ES+: 359.2(MH+, 100).

9-Benzyl-3-oxa-7,9-diazabicyclo[3.3.1]nonane



7-Benzenesulfonyl-9-benzyl-3-oxa-7,9-diazabicyclo[3.3.1]nonane (400mg; 1.1 mmol) was dissolved in xylene (8 ml), Red-Al (~3.5 M in toluene; 0.8 ml; 2.8 mmol) added and refluxed for 1.5 h. A second portion of Red-Al (0.4 ml; 1.4 mmol) was added and refluxed for another 30 min. The reaction mixture was poured on 2N HCl (100 ml) and washed twice with TBME. NaOH conc was added to the aqueous phase and extracted with TBME/EtOH (50:1) three times. The combined organic phases were dried with K2CO3, filtered, evaporated to dryness

and purified via chromatography (SiO2, EtOAc/MeOH/NH3conc 80/20/4) to yield the title compound as yellowish oil, which crystallised in needles (206 mg; 84 %).
1H-NMR (400MHz; DMSO-d6), δ (ppm): 2.27(s, 2H); 2.84(d, 2H); 3.16(bd, 2H); 3.79(d, 2H); 3.98(s, 2H); 4.03(d, 2H); 7.13-7.40(m, 5H).
MS (m/z) ES+: 219.1(MH+, 100).

3-Oxa-7,9-diazabicyclo[3.3.1]nonane-7,9-dicarboxylic acid di-tert-butyl ester

9-Benzyl-3-oxa-7,9-diazabicyclo[3.3.1]nonane (205 mg; 0.94 mmol) was dissolved in TBME (4 ml) and treated with (BOC)2O (500 mg; 2.2 mmol) in TBME (2 ml) at room temp. for 10 min. The reaction mixture was evaporated, taken up in EtOH (150 ml), Pd/C (10%; 350 mg) was added and hydrogenated for 2 h at 1 atm of H2. After filtration, evaporation to dryness and chromatography (SiO2, TBME/MeOH/NH3conc 90/10/2), the title compound was obtained as colorless crystals (186 mg; 60 %).
1H-NMR (400MHz; DMSO-d6), δ (ppm), mixture of rotamers: 1.40(s, 9H); 1.52(s, 9H); 2.95(bt, 1H); 3.10(bd, 1H); 3.58(bt, 2H); 3.82(bt, 4H); 4.05(bd, 1H); 4.15(bd, 1H).
The HSQC spectrum is in agreement with the structure.
MS (m/z) ES+: 351.2 (M+Na, 100).

7-(4-Fluorobenzyl)-3-oxa-7,9-diazabicyclo[3.3.1]nonane

3-Oxa-7,9-diazabicyclo[3.3.1]nonane-7,9-dicarboxylic acid di-tert-butyl ester (80 mg; 0.24 mmol) was dissolved in EtOH (0.5 ml) and treated with HClconc (0.5 ml) for 30 min. The reaction mixture was evaporated, taken up in EtOH (4 ml), NaHCO3 (102 mg; 1.2 mmol) added, followed by 4-fluorobenzylchloride (0.029 ml; 0.24 mml) and refluxed for 1.5 h. The

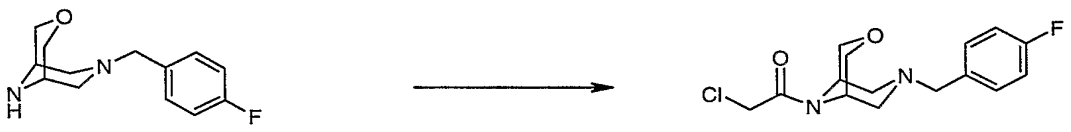
reaction mixture was evaporated and purified by chromatography (SiO2; TBME > TBME/MeOH/NH3conc 90/10/2) to yield the title compound as a yellowish foam (42 mg; 72 %).

1H-NMR (400MHz; DMSO-d6), δ (ppm): 2.33(bd, 2H); 2.72(bs, 2H); 2.80(d, 2H); 3.47(s, 2H); 3.63-3.74(m, 4H); 7.13(t, 2H); 7.38(dd, 2H).

The ROESY spectrum is in agreement with the structure.

MS (m/z) ES+: 237.2(MH+, 100).

2-Chloro-1-[7-(4-fluorobenzyl)-3-oxa-7,9-diazabicyclo[3.3.1]non-9-yl]-ethanone

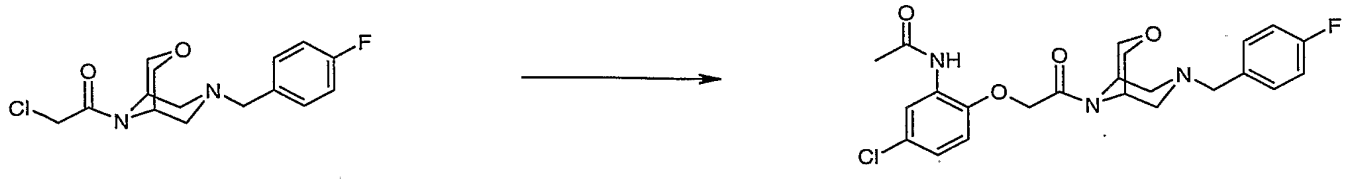


7-(4-Fluorobenzyl)-3-oxa-7,9-diazabicyclo[3.3.1]nonane (40 mg; 0.16 mmol) was dissolved in CH2Cl2 and treated with chloroacetylchloride (0.014 ml; 0.16 mmol). After 5 min. at room temp. the reaction mixture was poured on 2N Na2CO3 and extracted with TBME three times. The combined organic phases were dried over Na2SO4, filtered and evaporated to yield the title compound (53 mg; 98 %).

1H-NMR (400MHz; DMSO-d6), δ (ppm): 2.22(bd, 1H); 2.42(bd, 1H); 2.92(dd, 2H); 3.42(dd, 2H); 3.58(bd, 1H); 3.73(bd, 1H); 3.82(d, 2H); 3.96(bs, 1H); 4.28(s, 1H); 4.38(s, 2H); 7.15(t, 2H); 7.37(dd, 2H).

MS (m/z) ES+: 313.1(MH+, 100).

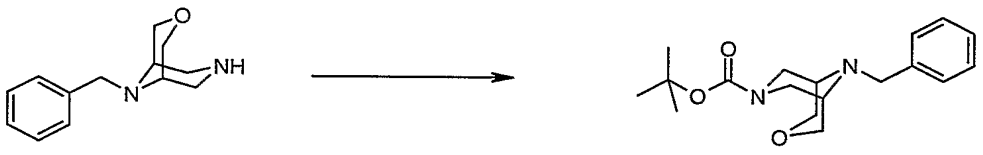
N-(5-Chloro-2-{2-[7-(4-fluorobenzyl)-3-oxa-7,9-diazabicyclo[3.3.1]non-9-yl]-2-oxoethoxy}-phenyl)acetamide



N-(5-Chloro-2-hydroxyphenyl)-acetamide (59 mg; 0.32 mmol) in THF (4 ml) was deprotonated with KN(TMS)2 (~0.8 M in toluene; 0.38 ml; 0.32 mmol) at room temp. for 10 min. 2-Chloro-1-[7-(4-fluorobenzyl)-3-oxa-7,9-diazabicyclo[3.3.1]non-9-yl]-ethanone (50 mg; 0.16 mmol) in THF (1 ml) was added to the resulting suspension and the mixture refluxed for 1 h, poured on 2N NaOH and extracted with TBME three times. The combined organic phases were dried over Na2SO4, filtered, evaporated
and purified via chromatography (acetone/hexanes (3/7 to 4/6) to yield the title compound as colorless crystals (52 mg; 70 %).
1H-NMR (400MHz; DMSO-d6), δ (ppm): 2.11(s, 3H); 2.26(d, 1H); 2.40(d, 1H); 2.89(d, 2H); 3.41(s, 2H); 3.60(d, 1H); 3.75(d, 1H); 3.80(d, 2H); 3.94(s, 1H); 4.29(s, 1H); 4.95(s, 2H); 7.00(d, 1H); 7.06(dd, 1H); 7.15(t, 2H); 7.36(dd, 2H); 8.12(bs, 1H); 9.54(s, 1H).
MS (m/z) ES+: 462.2(MH+, 100).

Example 11: N-(5-Chloro-2-{2-[9-(4-fluorobenzyl)-3-oxa-7,9-diazabicyclo[3.3.1]non-7-yl]-2-oxoethoxy}-phenyl)acetamide

9-Benzyl-3-oxa-7,9-diazabicyclo[3.3.1]nonane-7-carboxylic acid tert-butyl ester



9-Benzyl-3-oxa-7,9-diazabicyclo[3.3.1]nonane (1.08 g; 4.9 mmol) in TBME (50 ml)was treated with (BOC)2O (1.1 g; 5.0 mmol) in TBME (4 ml) for 1h at room temp. The reaction mixture was evaporated and purified via chromatography (TBME/hexanes 2/8 to 3/7) to yield the title compound as colorless crystals (1.45 g; 92 %).
1H-NMR (400MHz; DMSO-d6), δ (ppm): 1.39(s, 9H); 2.50(s, 2H); 3.26(d, 1H); 3.44(d, 1H); 3.69(dd, 2H); 3.75(d, 2H); 3.82(d, 2H); 3.92(s, 2H); 7.23(t, 1H); 7.32(t, 2H); 7.37(d, 2H).
MS (m/z) ES+: 319.2 (MH+, 100).

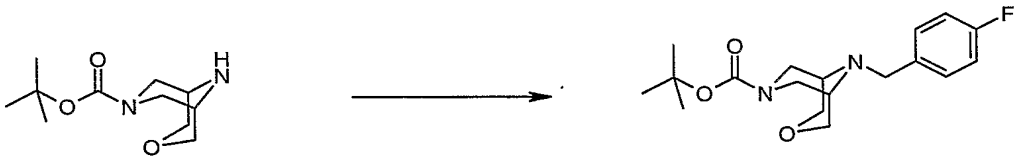
3-Oxa-7,9-diazabicyclo[3.3.1]nonane-7-carboxylic acid tert-butyl ester

9-Benzyl-3-oxa-7,9-diazabicyclo[3.3.1]nonane-7-carboxylic acid tert-butyl ester (100 mg; 0.3 mmol) in EtOH (150 ml) was hydrogenated over Pd/C (10%; 250 mg) at 1 atm and room temp. for 1 h. After filtration and evaporation of the solvent, the residue was purified via chromatography (TBME/MeOH/NH3conc 95/5/0.5 to 90/10/2) to yield the title compound as colorless crystals (53 mg; 74 %).

1H-NMR (400MHz; DMSO-d6), δ (ppm): 1.38(s, 9H); 2.64(bd, 2H); 3.03 (bd, 1H); 3.17(bd, 1H); 3.71(m, 4H); 3.92(d, 1H); 3.99(d, 1H); 6.67(bs, 0.5H); 7.27(bs, 0.5H).

MS (m/z) ES+: 229.1(MH+, 100).

9-(4-Fluorobenzyl)-3-oxa-7,9-diazabicyclo[3.3.1]nonane-7-carboxylic acid tert-butyl ester

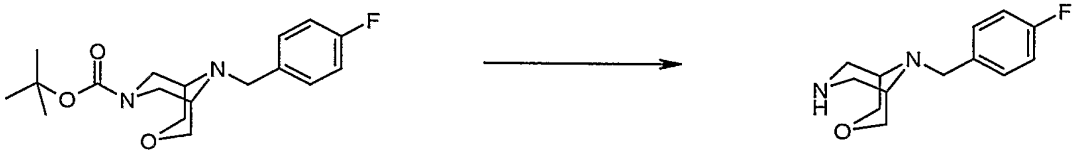


3-Oxa-7,9-diazabicyclo[3.3.1]nonane-7-carboxylic acid tert-butyl ester (97 mg; 0.4 mmol) in EtOH (4 ml) was combined with 4-fluorbenzylchlorid (0.051 ml; 0.4 mmol) and NaHCO3 (179 mg; 2.1 mmol) and refluxed for 1.5 h. The reaction mixture was evaporated, taken up in TBME, filtered and purifed via chromatography ((TBME/hexanes 2/8 to 3/7) to yield the title compound as colorless crystals (95 mg; 67 %)

1H-NMR (400MHz; DMSO-d6), δ (ppm): 1.40(s, 9H); 2.50(s, 2H); 3.28(d, 1H); 3.42(d, 1H); 3.68(dd, 2H); 3.73-3.88(m, 4H); 3.91(s, 2H); 7.13(t, 2H); 7.41(dd, 2H).

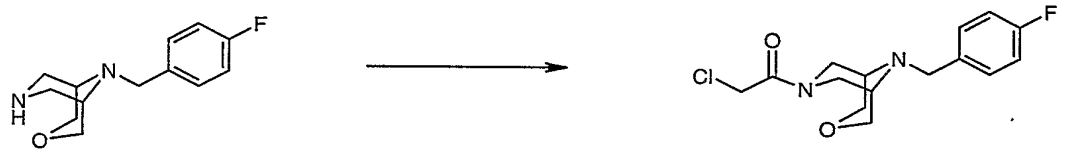
MS (m/z) ES+: 337.2(MH+, 100).

9-(4-Fluorobenzyl)-3-oxa-7,9-diazabicyclo[3.3.1]nonane



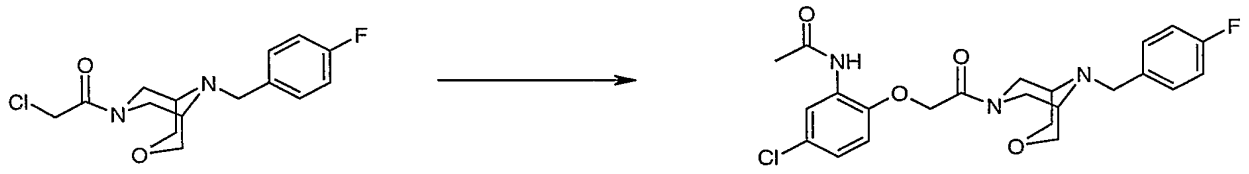
9-(4-Fluorobenzyl)-3-oxa-7,9-diazabicyclo[3.3.1]nonane-7-carboxylic acid tert-butyl ester (90 mg; 0.26 mmol) was dissolved in EtOH (4 ml) and treated with HCl conc (6 ml) for 5 min. The reaction mixture was poured on 2N NaOH/brine and extracted with TBME/THF (1:1) three times. The organic phases were combined, dried over K2CO3 and evaporated to dryness to yield the title compound as yellow resin (78 mg; 88 %)
1H-NMR (400MHz; DMSO-d6), δ (ppm): 2.26(s, 2H); 2.81(d, 2H); 3.17(d, 2H); 3.79(d, 2H); 3.95(s, 2H); 4.00(d, 2H); 7.13(t, 2H); 7.40(dd, 2H).
MS (m/z) ES+: 237.1(MH+, 100).

2-Chloro-1-[9-(4-fluorobenzyl)-3-oxa-7,9-diazabicyclo[3.3.1]non-7-yl]-ethanone



9-(4-Fluorobenzyl)-3-oxa-7,9-diazabicyclo[3.3.1]nonane (75 mg; 0.26 mmol) in CH2Cl2 (4 ml) was treated with chloroacetylchloride (0.022 ml; 0.26 mmol) for 5min., poured on 2N Na2CO3 and extracted with TBME three times. The combined organic phases were dried over Na2SO4, filtered and evaporated to dryness to yield the title compound as yellow foam (93 mg; 100%), which was used in the next step without further purification.
1H-NMR (400MHz; DMSO-d6), δ (ppm): 2.60(s, 2H); 3.22(d, 1H); 3.62(d, 1H); 3.69(s, 2H); 3.80(d, 2H); 3.87(d, 1H); 3.93(s, 2H); 4.16(d, 1H); 4.30(d, 1H); 4.43(d, 1H); 7.15(t, 2H); 7.43(dd, 2H).
MS (m/z) ES+: 313.1(MH+, 30).

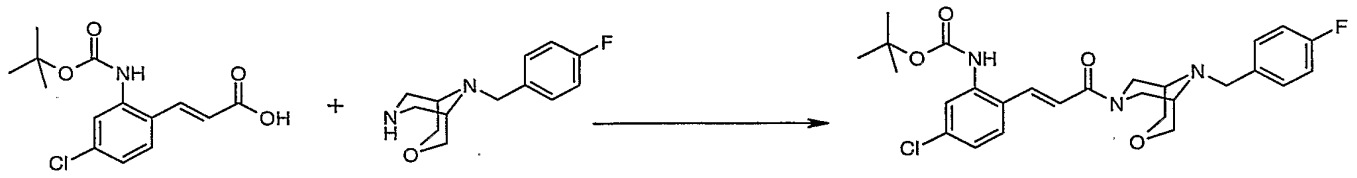
N-(5-Chloro-2-{2-[9-(4-fluorobenzyl)-3-oxa-7,9-diazabicyclo[3.3.1]non-7-yl]-2-oxoethoxy}-phenyl)acetamide



2-Chloro-1-[9-(4-fluorobenzyl)-3-oxa-7,9-diazabicyclo[3.3.1]non-7-yl]-ethanone (90 mg; 0.29 mmol) was reacted with N-(5-chloro-2-hydroxyphenyl)-acetamide as described in Example 10 to yield the title compound as colorless foam (83 mg; 62 %).
1H-NMR (400MHz; DMSO-d6), δ (ppm): 2.12(s, 3H); 3.22(d, 1H); 3.66(m, 4H); 3.78-3.90(m, 4H); 3.95(s, 2H); 4.20(d, 1H); 4.87(d, 1H); 5.00(d, 1H); 6.97-7.07(m, 2H); 7.16(t, 2H); 7.42(dd, 2H); 8.15(bs, 1H); 9.68(s, 1H).
MS (m/z) ES+: 462.2(MH+, 30).

Example 12: (E)-N-(5-Chloro-2-{3-[9-(4-fluorobenzyl)-3-oxa-7,9-diazabicyclo[3.3.1]non-7-yl]-3-oxopropenyl}-phenyl)-acetamide

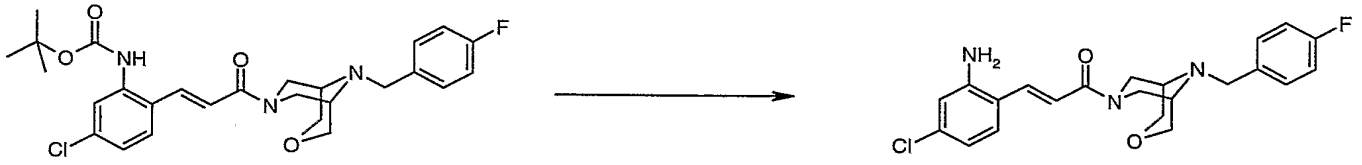
(E)-(5-Chloro-2-{3-[9-(4-fluorobenzyl)-3-oxa-7,9-diazabicyclo[3.3.1]non-7-yl]-3-oxopropenyl}-phenyl)-carbamic acid tert-butyl ester



9-(4-Fluorobenzyl)-3-oxa-7,9-diazabicyclo[3.3.1]nonane 100 mg; 0.44 mmol) and (E)-3-(2-tert-butoxycarbonylamino-4-chlorophenyl)-acrylic acid (133 mg; 0.44 mmol) were combined in CH2Cl2 (4 ml) and treated with EDCI.HCl (85 mg; 0.4 mmol) over night at room temp. The reaction mixture was poured on a column of SiO2 and chromatographed (acetone/hexanes 3/7) to yield the title compound as a colorless foam (167 mg; 73 %).

1H-NMR (400MHz; DMSO-d6), δ (ppm): 1.48(s, 9H); 2.64(bd, 2H); 3.28(bd, 2H); 3.65-3.78(m, 2H); 3.83(m, 2H); 3.97(s, 2H); 4.20(d, 1H); 4.36(d, 1H); 7.13-7.20(m, 3H); 7.25(dd, 1H); 7.46(m, 3H); 7.63(d, 1H); 7.88(d, 1H); 9.25(s, 1H).
MS (m/z) ES+: 516.1 (MH+, 30).

(E)-3-(2-Amino-4-chlorophenyl)-1-[9-(4-fluorobenzyl)-3-oxa-7,9-diazabicyclo[3.3.1]non-7-yl]-propenone



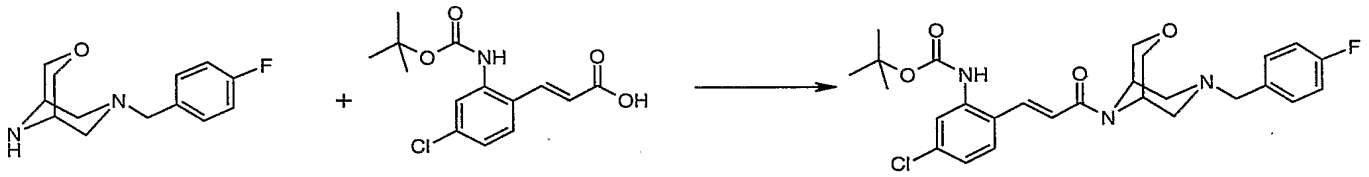
(E)-(5-Chloro-2-{3-[9-(4-fluorobenzyl)-3-oxa-7;9-diazabicyclo[3.3.1]non-7-yl]-3-oxopropenyl}-phenyl)-carbamic acid tert-butyl ester (40 mg; 0.08 mmol) was dissolved in EtOH (1 ml) and treated with HClconc (1 ml) for 2 min. at room temp. The reaction mixture was poured on a saturated solution of Na2CO3 and extracted with TBME three times. The combined organic phases were dried over Na2SO4, filtered and evaporated to dryness yield the title compound as a yellow foam (24 mg; 75 %).
1H-NMR (400MHz; DMSO-d6), δ (ppm): 2.65(bd, 2H); 3.30(m, 2H); 3.70(bt, 2H); 3.82(m, 2H); 3.98(s, 2H); 4.13(d, 1H); 4.34(d, 1H); 5.72(s, 2H, NH2); 6.55(dd, 1H); 6.73(d, 1H); 7.00(d, 1H); 7.17(t, 2H); 7.45(dd, 2H); 7.53(d, 1H); 7.62(d, 1H).
MS (m/z) ES+: 416.1 (MH+, 50).

(E)-N-(5-Chloro-2-{3-[9-(4-fluorobenzyl)-3-oxa-7,9-diazabicyclo[3.3.1]non-7-yl]-3-oxopropenyl}-phenyl)-acetamide

(E)-3-(2-Amino-4-chlorophenyl)-1-[9-(4-fluorobenzyl)-3-oxa-7,9-diazabicyclo[3.3.1]non-7-yl]-propenone (30 mg; 0.07 mmol) was reacted with acetylchloride and worked up as described in Example 1 to yield the title compound as colorless crystals (13 mg; 41 %).
1H-NMR (400MHz; DMSO-d6), δ (ppm): 2.08(s, 3H); 2.63(bd, 2H); 3.68(bt, 2H); 3.81(m, 4H); 3.95(s, 2H); 4.13(d, 1H); 4.32(d, 1H); 7.13-7.32(m, 4H); 7.43(m, 2H); 7.55(s, 1H); 7.58(d, 1H); 7.88(d, 1H); 9.90(s, 1H).
MS (m/z) ES+: 458.2(MH+, 50).

Example 13: (E)-N-(5-Chloro-2-{3-[7-(4-fluorobenzyl)-3-oxa-7,9-diazabicyclo[3.3.1]non-9-yl]-3-oxopropenyl}-phenyl)-acetamide

(E)-(5-Chloro-2-{3-[7-(4-fluorobenzyl)-3-oxa-7,9-diazabicyclo[3.3.1]non-9-yl]-3-oxopropenyl}-phenyl)-carbamic acid tert-butyl ester

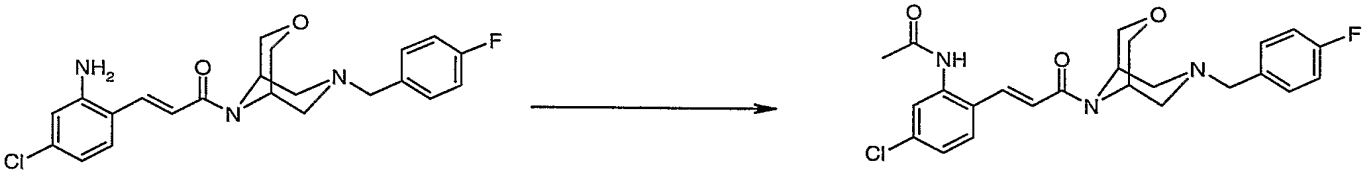


3-Oxa-7,9-diazabicyclo[3.3.1]nonane-7-carboxylic acid tert-butyl ester (154 mg; 0.65 mmol) and (E)-3-(2-tert-butoxycarbonylamino-4-chlorophenyl)-acrylic (193 mg; 0.65 mmol) in CH2Cl2 (4 ml) were combined with EDCI.HCl and kept overnight at room temp., poured on a silica gel column and chromatographed (acetone/hexanes 2/8) to yield the title compound as colorless crystals (286 mg; 85 %).
1H-NMR (400MHz; DMSO-d6), δ (ppm): 1.48(s, 9H); 2.28(d, 1H); 2.37(d, 1H); 2.98(bt, 2H); 3.45(dd, 2H); 3.62(bd, 1H); 3.68(bd, 1H); 3.88(d, 2H); 4.45(bd, 2H); 7.13-7.22(m, 3H); 7.26(dd, 1H); 7.39(dd, 2H); 7.47(s, 1H); 7.22(d, 1H); 7.90(d, 1H); 9.25(s, 1H).
MS (m/z) ES+: 516.1(MH+, 100).

(E)-3-(2-Amino-4-chlorophenyl)-1-[7-(4-fluorobenzyl)-3-oxa-7,9-diazabicyclo[3.3.1]non-9-yl]-propenone

(E)-(5-Chloro-2-{3-[7-(4-fluorobenzyl)-3-oxa-7,9-diazabicyclo[3.3.1]non-9-yl]-3-oxopropenyl}-phenyl)-carbamic acid tert-butyl ester (280 mg; 0.54 mmol) was dissolved in EtOH (2 ml) and treated with HClconc (2 ml) and kept at room temp. for 2 min. The reaction mixture was poured on a saturated solution of Na2CO3 and extracted with TBME three times. The combined organic phases were dried over Na2SO4, filtered and evaporated to dryness yield the title compound as a yellow foam (229 mg; 100 %).
1H-NMR (400MHz; DMSO-d6), δ (ppm): 2.27(d, 1H); 2.35(d, 1H); 2.97(dd, 2H); 3.43(dd, 2H); 3.63(d, 1H); 3.69(d, 1H); 3.88(dd, 2H); 4.38(s, 1H); 4.45(s, 1H); 5.78(s, 2H, NH2); 6.54(dd, 1H); 6.73(d, 1H); 6.98(d, 1H); 7.17(t, 2H); 7.40(dd, 2H); 7.56(d, 1H); 7.71 (d, 1H).
MS (m/z) ES+: 416.1(MH+, 100).

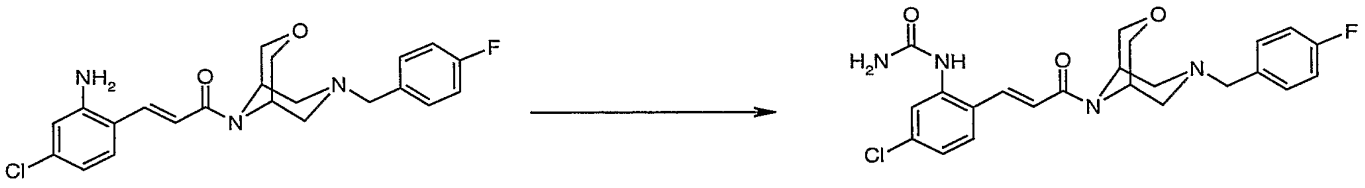
(E)-N-(5-Chloro-2-{3-[7-(4-fluorobenzyl)-3-oxa-7,9-diazabicyclo[3.3.1]non-9-yl]-3-oxopropenyl}-phenyl)-acetamide



(E)-3-(2-Amino-4-chlorophenyl)-1-[7-(4-fluorobenzyl)-3-oxa-7,9-diazabicyclo[3.3.1]non-9-yl]-propenone (280 mg; 0.5 mmol) was reacted with acetylchloride and worked up as described in Example 1 to yield the title compound as colorless crystals (20 mg; 36 %).
1H-NMR (400MHz; DMSO-d6), δ (ppm): 2.21(s, 3H); 2.28(d, 1H); 2.37(d, 1H); 2.98(t, 2H); 3.43(dd, 2H); 3.63(d, 1H); 3.68(d, 1H); 3.88(d, 2H); 4.45(bd, 2H); 7.15-7.22(m, 3H); 7.30(dd, 1H); 7.40(dd, 2H); 7.58(d, 1H); 7.71(d, 1H); 7.94(d, 1H); 9.93(s, 1H).

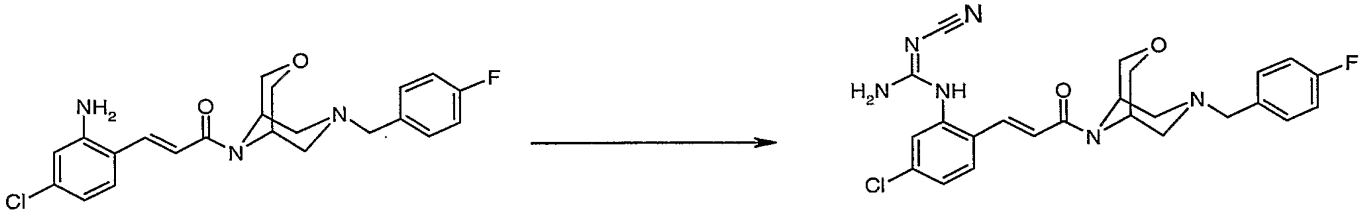
MS (m/z) ES+: 458.2 (MH+, 100).

Example 14: (E)-N-(5-Chloro-2-{3-[7-(4-fluorobenzyl)-3-oxa-7,9-diazabicyclo[3.3.1]non-9-yl]-3-oxopropenyl}-phenyl)-urea



(E)-3-(2-Amino-4-chlorophenyl)-1-[7-(4-fluorobenzyl)-3-oxa-7,9-diazabicyclo[3.3.1]non-9-yl]-propenone (50 mg; 0.12 mmol) was reacted with NaOCN and worked up as described in Example 4 to yield the title compound as colorless crystals (23 mg; 43 %).
1H-NMR (400MHz; DMSO-d6), δ (ppm): 2.28(d, 1H); 2.38(d, 1H); 2.97(dd, 2H); 3.43(dd, 2H); 3.63(d, 1H); 3.66(d, 1H); 3.88(d, 2H); 4.45 (m, 2H); 6.28(s, 2H, NH2); 7.07(dd, 1H); 7.13-7.21(m, 3H); 7.49(dd, 2H); 7.73(d, 1H); 7.78(d, 1H); 7.97(d, 1H); 8.43(s, 1H).
MS (m/z) ES+: 459.2 (MH+, 100).

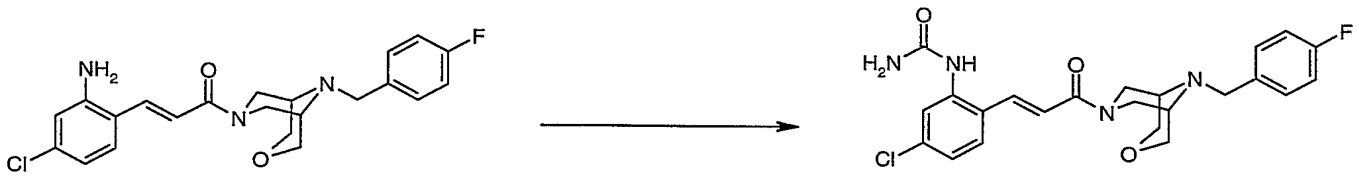
Example 15: (E)-N-(5-Chloro-2-{3-[7-(4-fluorobenzyl)-3-oxa-7,9-diazabicyclo[3.3.1]non-9-yl]-3-oxopropenyl}-phenyl)-N'cyanoguanidine



(E)-3-(2-Amino-4-chlorophenyl)-1-[7-(4-fluorobenzyl)-3-oxa-7,9-diazabicyclo[3.3.1]non-9-yl]-propenone (50 mg; 0.12 mmol) was reacted with NaN(CN)2 as described in Example 2 and yielded the title compound as colorless crystals (15 mg; 26 %).

1H-NMR (400MHz; DMSO-d6), δ (ppm): 2.25(d, 1H); 2.33(d, 1H); 2.96(bt, 2H); 3.41(d, 2H); 3.60(d, 1H); 3.67(d, 1H); 3.85(d, 2H); 4.42(m, 2H); 7.17(t, 2H); 7.23(d, 1H); 7.32-7.42(m, 3H); 7.47(s, 1H); 7.60(d, 1H); 7.94(d, 1H); 9.00(s, 1H).
MS (m/z) ES+: 483.1(MH+, 100).

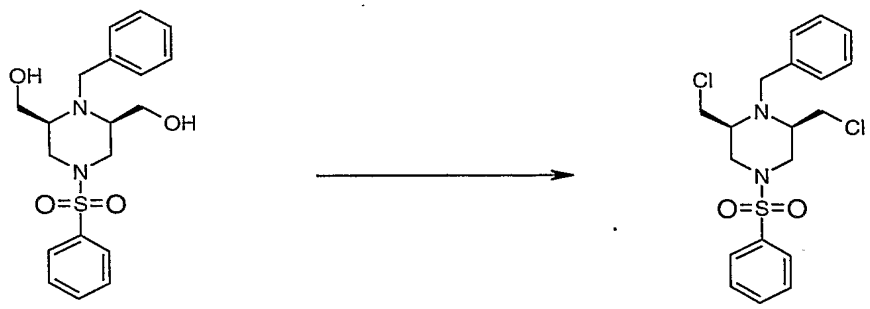
Example 16: (E)-(5-Chloro-2-{3-[9-(4-fluorobenzyl)-3-oxa-7,9-diazabicyclo[3.3.1]non-7-yl]-3-oxopropenyl}-phenyl)-urea



(E)-3-(2-Amino-4-chlorophenyl)-1-[9-(4-fluorobenzyl)-3-oxa-7,9-diazabicyclo[3.3.1]non-7-yl]-propenone (30 mg; 0.07 mmol) was reacted with NaOCN and worked up as described in Example 4 to yield the title compound as colorless crystals (35 mg; 37 %).
1H-NMR (400MHz; DMSO-d6), δ (ppm): 2.63(d, 2H); 3.30(d, 2H); 3.67-3.76(m, 2H); 3.82(m, 2H); 3.98(s, 2H); 4.17(d, 1H); 4.37(d, 1H); 6.25(s, 2H; 7.07(dd, 1H); 7.13-7.21(m, 3H); 7.45(dd, 2H); 7.67(d, 1H); 7.77(d, 1H); 7.99(d, 1H); 8.41(s, 1H).
MS (m/z) ES+: 459.2(MH+, 100).

Example 17: 9-[2-(2-Acetylamino-4-chloro-phenoxy)-acetyl]-7-(4-fluorobenzyl)-3,7,9-triazabicyclo[3.3.1]nonane-3-carboxylic acid tert-butyl ester

(meso)-4-Benzenesulfonyl-1-benzyl-2,6-bis-chloromethylpiperazine

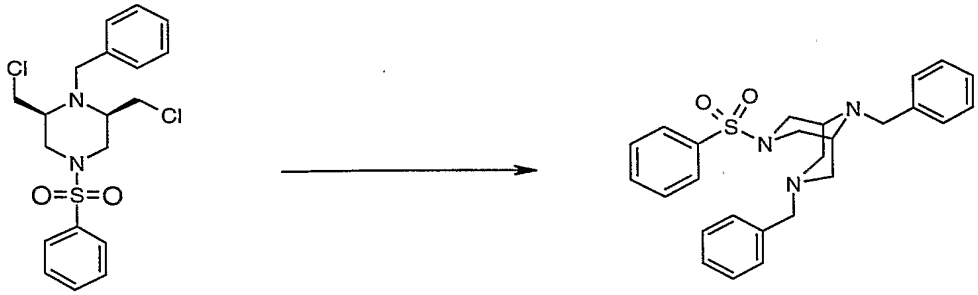


Thionylchloride (10 ml; 137 mmol) was rapidly added under stirring to an ice-cooled solution of *(meso)*-(4-benzenesulfonyl-1-benzyl-6-hydroxymethyl-piperazin-2-yl)-methanol (10 g; 26 mmol) in DMF (200 ml). The reaction mixture was warmed to room temp., stirred for 1 h and poured on a saturated solution of Na2CO3 (1000 ml). The precipitated solid was filtered off, washed with water and recrystallised from TBME to yield the title compound as colorless crystals (8.5 g; 77 %).

1H-NMR (400MHz; DMSO-d6), δ (ppm): 2.50-2.60(m, 2H); 2.93-3.00(m, 2H); 3.51-3.58(m, 4H); 3.77(d, 2H); 3.93(s, 2H); 7.22-7.33(m, 5H); 7.68(t, 2H); 7.74-7.83(m, 3H).

MS (m/z) EI-MS: 412(M+, 50); 377(20); 271(55); 235(30); 91(100); 77(20).

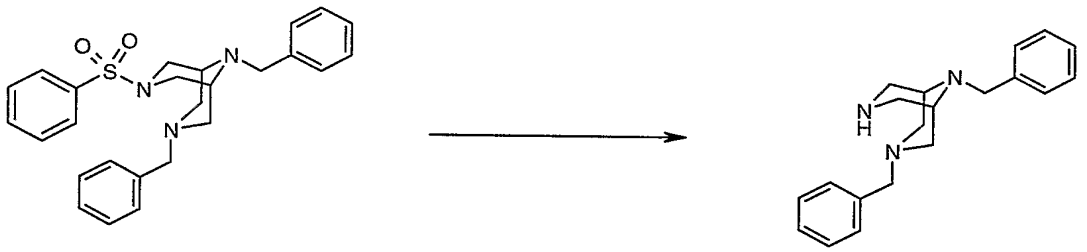
3-Benzenesulfonyl-7,9-dibenzyl-3,7,9-triazabicyclo[3.3.1]nonane



(meso)-4-Benzenesulfonyl-1-benzyl-2,6-bis-chloromethylpiperazine (610 mg; 1.5 mmol) and benzylamine (12 ml) were refluxed in an oil bath (200 °C) for 15 min. The reaction mixture was poured on water and extracted with EtOAc three times. The combined organic phases were dried over Na2SO4, filtered and evaporated to dryness and purified via chromatography (SiO2; TBME/hexanes 2/8) to yield the title compound as colorless crystals (488 mg; 74 %)

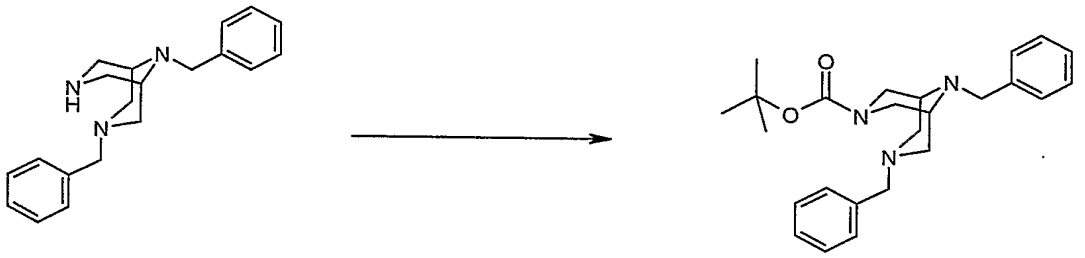
1H-NMR (400MHz; DMSO-d6), δ (ppm): 2.53(d, 2H); 2.69(d, 2H); 2.81(d, 2H); 2.83(s, 2H); 3.41(d, 2H); 3.44(s, 2H); 3.67(s, 2H); 7.16-7.32(m, 8H); 7.38(m, 2H); 7.65-7.78(m, 5H).
MS (m/z) ES+: 448.2 (MH+, 100).

3,9-Dibenzyl-3,7,9-triazabicyclo[3.3.1]nonane



3-Benzenesulfonyl-7,9-dibenzyl-3,7,9-triazabicyclo[3.3.1]nonane (488 mg; 1.1 mmol) was dissolved in xylene (10 ml), Red-Al (~3.5 M in toluene; 1.25 ml; 4.4 mmol) added and refluxed for 1 h. The reaction mixture was poured on NaOH conc. and extracted with THF three times. The combined organic phases were dried with K2CO3, filtered, evaporated to dryness and purified via chromatography (SiO2, EtOAc/MeOH/NH3conc 80/20/4) to yield the title compound as a yellowish oil, which slowly crystallised on standing (276 mg; 82 %).
MS (m/z) ES+: 308.2(MH+, 100).

7,9-Dibenzyl-3,7,9-triazabicyclo[3.3.1]nonane-3-carboxylic acid tert-butyl ester



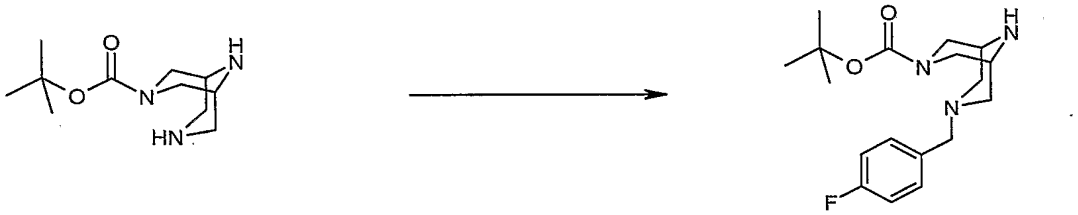
3,9-Dibenzyl-3,7,9-triazabicyclo[3.3.1]nonane (276 mg; 0.9 mmol) were dissolved in TBME (4 ml) and treated with (BOC)2O (216 mg; 1 mmol) for 10 min at room temp. The reaction mixture was diluted with hexanes and purified via chromatography (SiO2, TBME/hexanes 2/8) to yield the title compound as colorless crystals (285 mg; 78 %).

1H-NMR (400MHz; DMSO-d6), δ (ppm): 1.45(s, 9H); 2.43(bt, 2H); 2.65-2.76(m, 3H); 3.23(bd, 1H); 3.35(s, 2H); 3.35-3.43(m, 2H); 3.70(d, 1H); 3.78(d, 1H); 3.88(s, 2H); 7.20-7.40(m, 10H).
MS (m/z) ES+: 408.3(MH+, 100).

3,7,9-Triazabicyclo[3.3.1]nonane-3-carboxylic acid tert-butyl ester

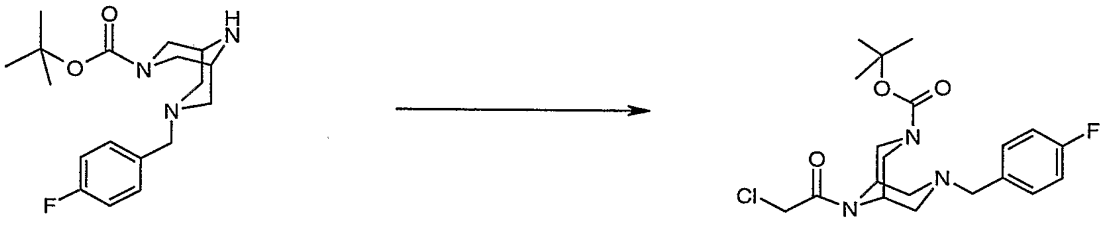
7,9-Dibenzyl-3,7,9-triazabicyclo[3.3.1]nonane-3-carboxylic acid tert-butyl ester (285 mg; 0.7 mmol) in EtOH (150 ml) was hydrogenated over Pd/C (10 %; 1 g) at 1 atm and room temp. for 4 h. Filtration, evaporation and chromatography (SiO2; TBME/MeOH/NH3conc 80/20/4 to 60/40/10) yielded the title compound (109 mg; 69 %) as a colorless resin.
MS (m/z) ES+: 228(MH+, 100).

7-(4-Fluorobenzyl)-3,7,9-triazabicyclo[3.3.1]nonane-3-carboxylic acid tert-butyl ester



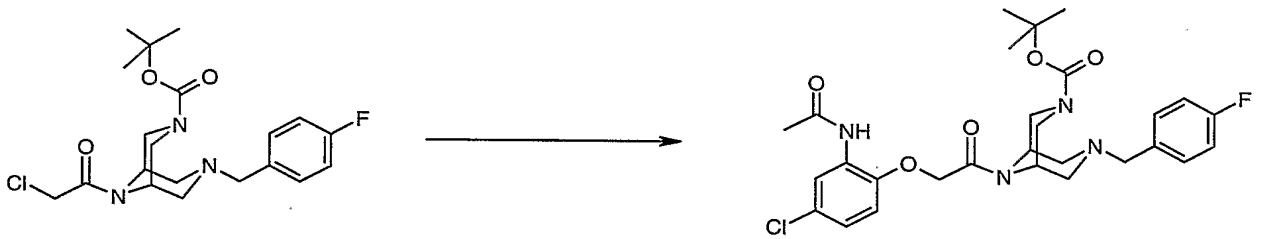
3,7,9-Triazabicyclo[3.3.1]nonane-3-carboxylic acid tert-butyl ester (39 mg; 0.17 mmol), 4-fluorobenzylchloride (0.02 ml; 0.17 mmol) and NaHCO3 (72 mg; 0.85 mmol) were combined and refluxed in EtOH for 2 h. Evaporation and chromatography (SiO2; TBME/MeOH/NH3conc 90/10/2) yielded the title compound as yellow crystals (32 mg; 55 %).
1H-NMR (400MHz; DMSO-d6), δ (ppm): 1.43(s, 9H); 2.18(d, 1H); 2.23(d, 1H); 2.78(d, 1H); 2.87(d, 1H); 2.98(d, 1H); 3.11(d, 1H); 3.25(d, 1H); 3.30(s, 2H); 3.22(d, 1H); 3.83(d, 1H); 3.90(d, 1H); 7.06(t, 2H); 7.33(dd, 2H).
MS (m/z) ES+: 336.3 (MH+, 100).

9-(2-Chloroacetyl)-7-(4-fluorobenzyl)-3,7,9-triazabicyclo[3.3.1]nonane-3-carboxylic acid tert-butyl ester



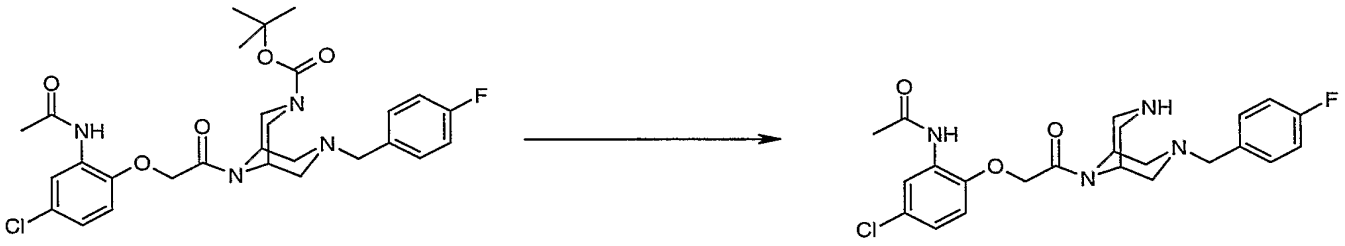
Chloroacetylchloride (0.008 ml; 0.1 mmol) was added to 7-(4-fluorobenzyl)-3,7,9-triazabicyclo[3.3.1]nonane-3-carboxylic acid tert-butyl ester (30 mg; 0.09 mmol) dissolved in THF (1 ml). After 5 min. at room temp. the reaction mixture was poured on 2N Na2CO3 and extracted with TBME three times. The combined organic phases were dried over Na2SO4, filtered, evaporated to dryness and yielded the title compound as a resin (38 mg; 100%) used in the next step without further purification.
MS (m/z) ES+: 412.2(MH+, 100).

9-[2-(2-Acetylamino-4-chloro-phenoxy)-acetyl]-7-(4-fluorobenzyl)-3,7,9-triazabicyclo[3.3.1]nonane-3-carboxylic acid tert-butyl ester



9-(2-Chloroacetyl)-7-(4-fluorobenzyl)-3,7,9-triazabicyclo[3.3.1]nonane-3-carboxylic acid tert-butyl ester (35 mg; 0.08 mmol) was reacted with N-(5-chloro-2-hydroxyphenyl)-acetamide as described in Example 10 to yield the title compound as colorless foam (32 mg; 65 %).
1H-NMR (400MHz; DMSO-d6), δ (ppm): 1.46(s, 9H); 2.10(s, 3H); 2.20(m, 1H); 2.33(bd, 1H); 2.90(bt, 2H); 3.03-3.17(m, 2H); 3.28(bd, 2H); 3.43(bd, 1H); 3.93-4.10(m, 3H); 4.95(s, 2H); 6.98(d, 1H); 7.05-7.15(m, 3H); 7.33(m, 2H); 8.10(s, 1H); 9.52(bd, 1H).
MS (m/z) ES+: 561.2(MH+, 30).

Example 18: N-(5-Chloro-2-{2-[3-(4-fluorobenzyl)-3,7,9-triazabicyclo[3.3.1]non-9-yl]-2-oxo-ethoxy}-phenyl)-acetamide



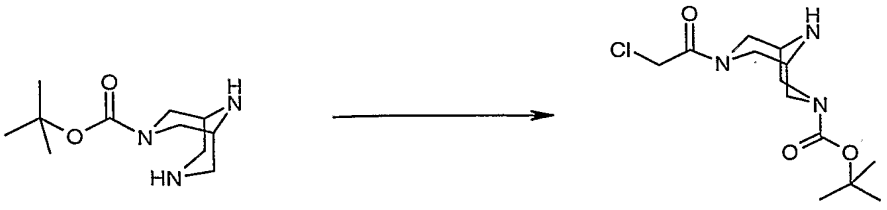
9-[2-(2-Acetylamino-4-chloro-phenoxy)-acetyl]-7-(4-fluorobenzyl)-3,7,9-triazabicyclo[3.3.1]nonane-3-carboxylic acid tert-butyl ester (23 mg; 0.04 mmol) in EtOH (1 ml) was treated with HClconc (1 ml) for 5 min. at room temp., poured on Na2CO3 conc. and extracted with TBME three times. The combined organic phases were dried over Na2SO4, filtered, evaporated to dryness and yielded the title compound as yellowish crystals (13 mg; 73 %).

1H-NMR (400MHz; DMSO-d6), δ (ppm): 2.10 (s, 3H); 2.25(bd, 1H); 2.30(bd, 1H); 2.67-3.00(m, 6H); 3.35(d, 2H); 3.78(s, 1H); 4.20(s, 1H); 4.91(s, 2H); 7.00(d, 1H); 7.08(dd, 1H); 7.17(t, 2H); 7.35(dd, 2H); 8.12(bs, 1H); 9.59(s, 1H).

MS (m/z) ES+: 461.2(MH+, 100).

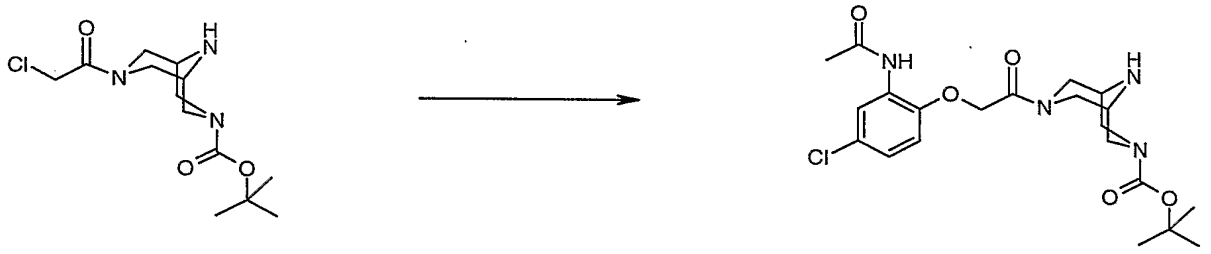
Example 19: 7-[2-(2-Acetylamino-4-chloro-phenoxy)-acetyl]-9-(4-fluorobenzyl)-3,7,9-triazabicyclo[3.3.1]nonane-3-carboxylic acid tert-butyl ester

7-(2-Chloroacetyl)-3,7,9-triazabicyclo[3.3.1]nonane-3-carboxylic acid tert-butyl ester



3,7,9-Triazabicyclo[3.3.1]nonane-3-carboxylic acid tert-butyl ester (20 mg; 0.09 mmol) in CH2Cl2 (2 ml) was treated with chloroacetylchloride (0.007 ml; 0.09 mmol) for 5 min. at room temp., evaporated and used in the next step without further purification.

7-[2-(2-Acetylamino-4-chloro-phenoxy)-acetyl]-3,7,9-triazabicyclo[3.3.1]nonane-3-carboxylic acid tert-butyl ester

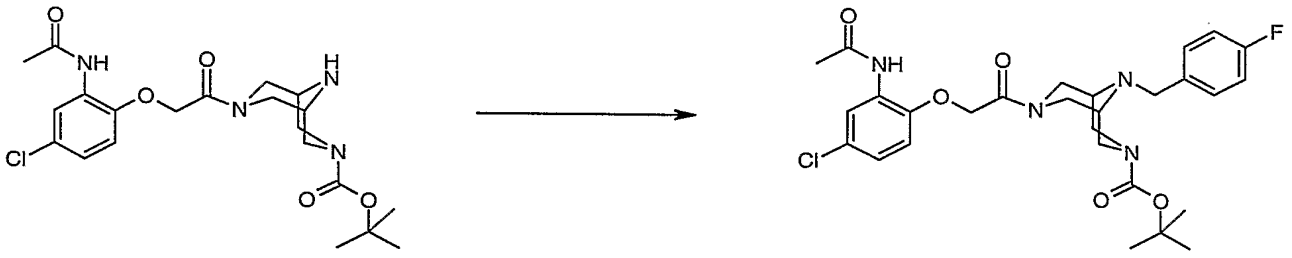


7-(2-Chloroacetyl)-3,7,9-triazabicyclo[3.3.1]nonane-3-carboxylic acid tert-butyl ester (27 mg; 0.09 mmol) was reacted with N-(5-chloro-2-hydroxyphenyl)-acetamide as described in Example 10 and purified via chromatography (SiO2; TBME/MeOH 9/1 then TBME/MeOH/NH3conc 80/20/4) to yield the title compound as almost colorless foam (23mg; 58 %).

1H-NMR (400MHz; DMSO-d6), δ (ppm): 1.30(s, 9H); 2.10(s, 3H); 2.87-3.13(m, 5H); 3.33(d, 1H); 3.71(d, 1H); 3.88(d, 1H); 4.10(d, 1H); 4.28(d, 1H); 4.76(d, 1H); 4.84(d, 1H); 7.09(s, 2H); 8.13(bs, 1H); 9.90(bs, 1H).

MS (m/z) ES+: 453.2(MH+, 100).

7-[2-(2-Acetylamino-4-chloro-phenoxy)-acetyl]-9-(4-fluorobenzyl)-3,7,9-triazabicyclo[3.3.1]nonane-3-carboxylic acid tert-butyl ester

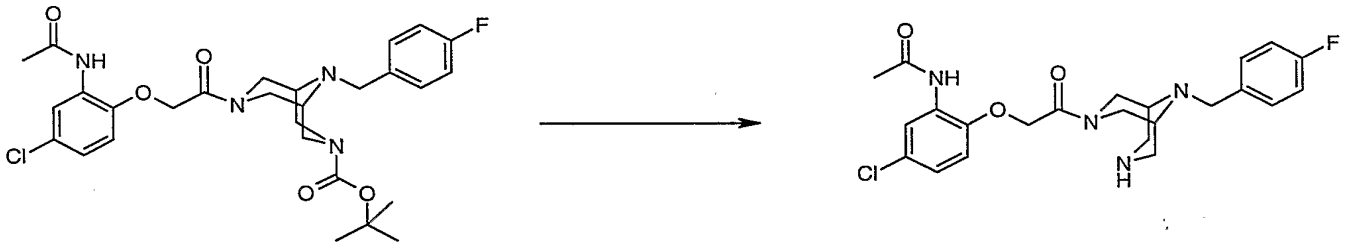


7-[2-(2-Acetylamino-4-chloro-phenoxy)-acetyl]-3,7,9-triazabicyclo[3.3.1]nonane-3-carboxylic acid tert-butyl ester (20 mg; 0.04 mmol), 4-fluorobenzylchloride (0.022 ml; 0.16 mmol) and K2CO3 (200 mg; 1.44 mmol) were combined and refluxed in EtOH (2 ml) for 14 h. The reaction mixture was poured on water and extracted with TBME three times. The combined organic phases were dried over Na2SO4, filtered, evaporated to dryness and purified via chromatography (SiO2; acetone/hexanes 3/7) to yield the title compound as colorless solid (14 mg; 56 %).

1H-NMR (400MHz; DMSO-d6), δ (ppm): 1.30(s, 9H); 2.12(s, 3H); 2.73(bs, 2H); 3.08-3.22(m, 3H); 3.50-3.65(m, 2H); 3.78(d, 1H); 3.92(s, 2H); 4.03(d, 1H); 4.17(d, 1H); 4.76(d, 1H); 4.86(d, 1H); 7.06(s, 2H); 7.15(t, 2H); 7.40(dd, 2H); 8.12(bd, 1H); 9.88(bd, 1H).

MS (m/z) ES+: 561.1(MH+, 30).

Example 20: N-(5-Chloro-2-{2-[9-(4-fluoro-benzyl)-3,7,9-triaza-bicyclo[3.3.1]non-3-yl]-2-oxo-ethoxy}-phenyl)-acetamide



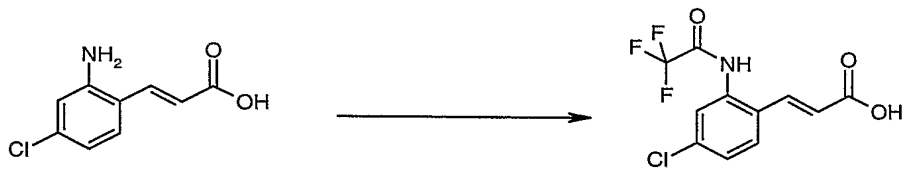
7-[2-(2-Acetylamino-4-chloro-phenoxy)-acetyl]-9-(4-fluorobenzyl)-3,7,9-triazabicyclo[3.3.1]nonane-3-carboxylic acid tert-butyl ester (10 mg; 0.001 mmol) was dissolved in EtOH (0.5 ml) and treated with HCl conc. (1 ml) for 2 min at room temp. The reaction mixture was poured on Na2CO3 conc. and extracted with TBME three times. The combined organic phases were dried over Na2SO4, filtered and evaporated to dryness to yield the title compound as yellow resin (5 mg; 65 %).

1H-NMR (400MHz; DMSO-d6), δ (ppm): 2.13(s, 3H); 2.58(bd, 2H); 2.76(bd, 1H); 2.88-3.00(m, 2H); 3.08(m, 1H); 3.5(d, 2H); 3.65(bd, 1H); 3.90(s, 2H); 4.03(s, 1H); 4.82(d, 1H); 5.03(d, 1H); 7.08(s, 2H); 7.15(t, 2H); 7.41(dd, 2H); 8.22(s, 1H); 9.88(s, 1H).

MS (m/z) ES+: 461.2(MH+, 100).

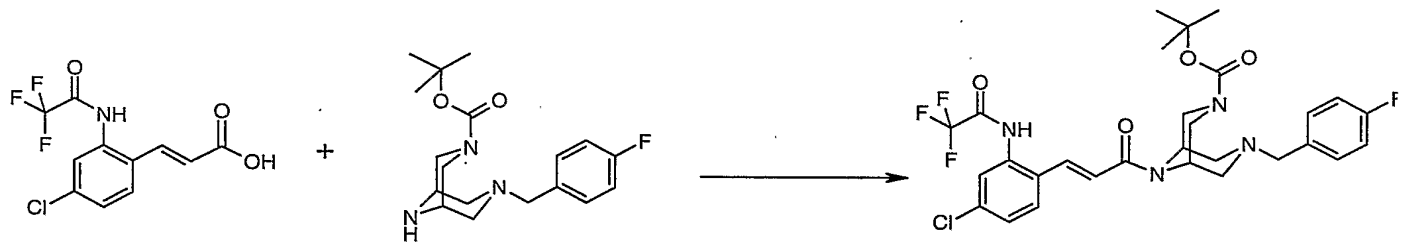
Example 21: (E)-N-(5-Chloro-2-{3-[3-(4-fluorobenzyl)-3,7,9-triazabicyclo[3.3.1]non-9-yl]-3-oxo-propenyl}-phenyl)-acetamide

(E)-3-[4-Chloro-2-(2,2,2-trifluoroacetylamino)-phenyl]-acrylic acid



(E)-3-(2-amino-4-chlorophenyl)-acrylic acid (200 mg; 0.67 mmol) (R.W.Carling et al., J. Med. Chem. (1997), 40(5), 754-765) in CH2Cl2 (6 ml) and NEt3 (0.19 ml; 1.3 mmol) was stirred, cooled to 0^0C and combined with TFAA (0.096 ml; 0.67 mmol). The reaction mixture was warmed to room temp., stirred for 10 min. poured on 2N HCl and extracted with TBME three times. The combined organic phases were dried over Na2SO4 and evaporated to dryness to yield the title compound as slightly yellow crystals (205 mg; 100%).
1H-NMR (400MHz; DMSO-d6), δ (ppm): 6.58(d, 1H); 7.46-7.50(m, 2H); 7.54(55, 1H); 7.93(d, 1H); 11.40(s, 1H); 12.5(s, 1H).
MS (m/z) ES-: 292.0 (M-H-; 100).

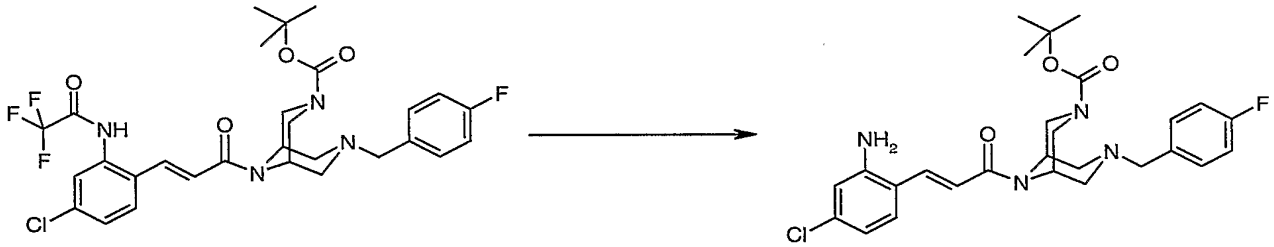
(E)-9-{3-[4-Chloro-2-(2,2,2-trifluoroacetylamino)-phenyl]-acryloyl}-7-(4-fluorobenzyl)-3,7,9-triazabicyclo[3.3.1]nonane-3-carboxylic acid tert-butyl ester



7-(4-Fluorobenzyl)-3,7,9-triazabicyclo[3.3.1]nonane-3-carboxylic acid tert-butyl ester (230 mg; 0.7 mmol), (E)-3-[4-chloro-2-(2,2,2-trifluoroacetylamino)-phenyl]-acrylic acid (205 mg; 0.7 mmol) and EDCI.HCl (134 mg; 0.7 mmol) in CH2Cl2 (4 ml) were stirred for 2 h at room

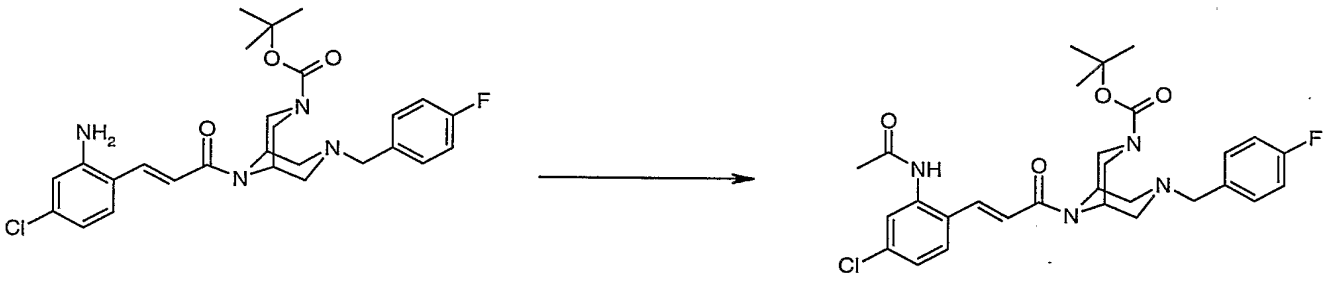
temp.; poured on a silica gel column and chromatographed (acetone/hexanes 15/85) to yield the title compound as colorless crystals (294 mg; 69 %).
1H-NMR (400MHz; DMSO-d6), δ (ppm): 1.47(s, 9H); 2.08(bd, 0.5H); 2.18(bt, 1H); 2.29(bd, 0.5H); 2.88-3.22(m, 4H); 3.27(d, 1H); 3.45(dd, 1H); 3.98(m, 2H); 4.48(m, 2H); 7.08(t, 2H); 7.23-7.37(m, 3H); 7.45-7.53(m, 3H); 8.03(dd, 1H); 11.4(s, 1H).
MS (m/z) ES+: 611.0(MH+, 100).

(E)-9-[3-(2-Amino-4-chlorophenyl)-acryloyl]-7-(4-fluorobenzyl)-3,7,9-triazabicyclo[3.3.1]nonane-3-carboxylic acid tert-butyl ester



(E)-9-{3-[4-Chloro-2-(2,2,2-trifluoroacetylamino)-phenyl]-acryloyl}-7-(4-fluorobenzyl)-3,7,9-triazabicyclo[3.3.1]nonane-3-carboxylic acid tert-butyl ester (240 mg; 0.39 mmol) in EtOH (14 ml) and 2N NaOH (5 ml) was refluxed for 1.5 h, poured on brine and extracted with TBME three times. The combined organic phases were dried over Na2SO4 and evaporated to dryness to yield the title compound as slightly yellow crystals (199 mg; 99 %).
1H-NMR (400MHz; DMSO-d6), δ (ppm): 1.45(s, 9H); 2.08(bd, 0.5H); 2.17(bt, 1H); 2.28(bd, 0.5H); 2.92(d, 1H); 2.96(d, 1H); 3.05(bt, 1H); 3.17(bd, 1H); 3.26(d, 1H); 3.42(d, 1H); 4.04(dd, 2H); 4.46(bs, 1H); 4.58(bs, 1H); 5.76(s, 2H, NH2). 6.52(bd, 1H); 6.71 (d, 1H); 6.96(dd, 1H); 7.08(t, 2H); 7.33(dd, 2H); 7.51(dd, 1H); 7.68(1H).
MS (m/z) ES+: 515.1(MH+, 100).

(E)-9-[3-(2-Acetylamino-4-chlorophenyl)-acryloyl]-7-(4-fluorobenzyl)-3,7,9-triazabicyclo[3.3.1]nonane-3-carboxylic acid tert-butyl ester

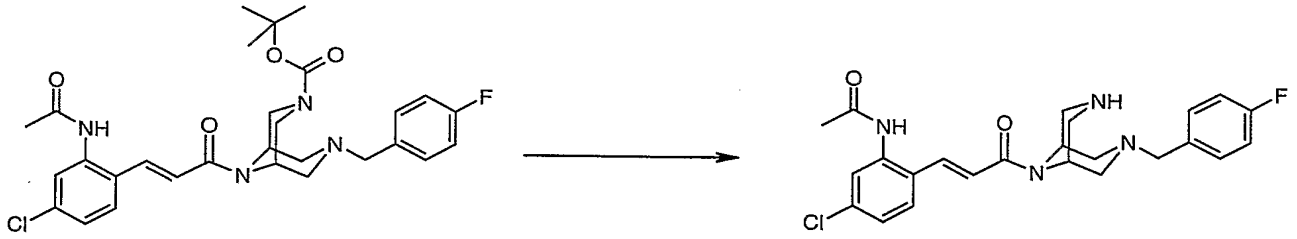


(E)-9-[3-(2-Amino-4-chlorophenyl)-acryloyl]-7-(4-fluorobenzyl)-3,7,9-triazabicyclo[3.3.1]nonane-3-carboxylic acid tert-butyl ester (43 mg; 0.08 mmol) in THF (4 ml) and NEt3 (0.12 ml; 0.83 mmol) was treated with acetylchloride (0.059 ml; 0.83 mmol) at reflux for 30 min., poured on 2N Na2CO3 and extracted with TBME three times. The combined organic phases were dried over Na2SO4, evaporated and purified by chromatography (SiO2, acetone/hexanes 2/8 to 3/7) to yield the title compound as colorless crystals (29 mg; 62 %).

1H-NMR (400MHz; DMSO-d6), δ (ppm): 1.45(s, 9H); 2.09(bs, 3.5H); 2.18(bt, 1H); 2.28(bd, 0.5H); 2.90-3.21(m, 4H); 3.38(d, 1H); 3.43(d, 1H); 4.06(dd, 2H); 4.50(bd, 1H); 4.58(bs, 1H); 7.08(t, 2H); 7.17(dd, 1H); 7.28(m, 1H); 7.33(dd, 2H); 7.56(bs, 1H); 7.68(bd, 1H); 7.90(m, 1H); 9.90(s, 1H).

MS (m/z) ES+: 557.1(MH+, 100).

<u>(E)-N-(5-Chloro-2-{3-[3-(4-fluorobenzyl)-3,7,9-triazabicyclo[3.3.1]non-9-yl]-3-oxo-propenyl}-phenyl)-acetamide</u>



(E)-N-(5-Chloro-2-{3-[3-(4-fluorobenzyl)-3,7,9-triazabicyclo[3.3.1]non-9-yl]-3-oxopropenyl}-phenyl)-acetamide (26 mg; 0.046 mmol) in CH2Cl2/TFA (1 ml /1 ml) was kept at room temp for 5 min. and then evaporated to dryness, taken up in EtOH, 2N Na2CO3 / 2N NaOH and extracted with TBME three times. The combined organic phases were dried over Na2SO4, evaporated and the remaining resin dissolved in a few drops of EtOH, diluted with TBME and

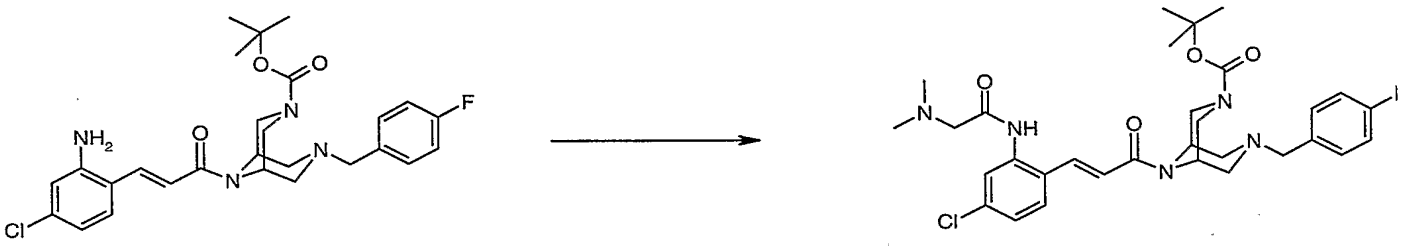
filtered from some precipitated impurity. Evaporation delivered the title compound as a colorless foam (20 mg; 90 %).

1H-NMR (400MHz; DMSO-d6), δ (ppm): 2.10(s, 3H); 2.28(m, 2H); 2.37(m, 2H); 2.75-3.06(m, 4H); 3.37(d, 2H); 4.28(s, 1H); 4.48(s, 1H); 7.08-7.18(m, 4H); 7.33-7.40(m, 2H); 7.55(s, 1H); 7.65(d, 1H); 7.90(m, 1H); 9.90(s, 1H).

MS (m/z) ES+: 457.1(MH+, 100).

Example 22: (E)-N-(5-Chloro-2-{3-[3-(4-fluorobenzyl)-3,7,9-triazabicyclo[3.3.1]non-9-yl]-3-oxopropenyl}-phenyl)-2-dimethylaminoacetamide

(E)-9-{3-[4-Chloro-2-(2-dimethylaminoacetylamino)-phenyl]-acryloyl}-7-(4-fluorobenzyl)-3,7,9-triazabicyclo[3.3.1]nonane-3-carboxylic acid tert-butyl ester

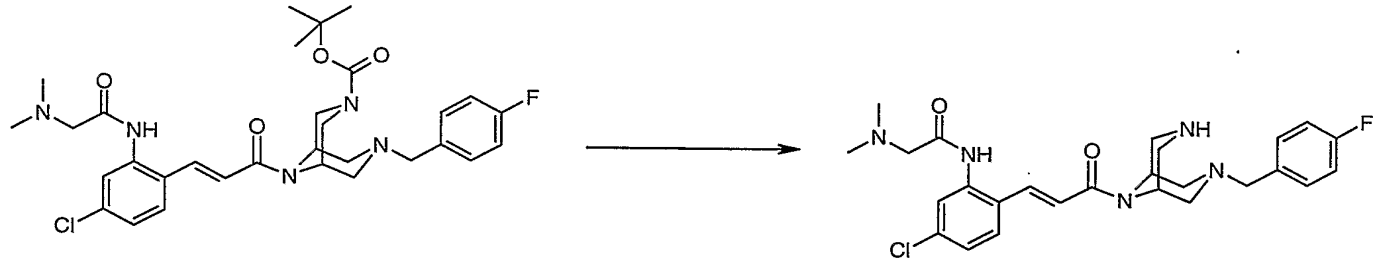


(E)-N-(5-Chloro-2-{3-[3-(4-fluorobenzyl)-3,7,9-triazabicyclo[3.3.1]non-9-yl]-3-oxopropenyl}-phenyl)-acetamide (80 mg; 0.16 mmol) dissolved in THF (1 ml) was treated with chloroacetylchloride (0.015 ml; 0.19 mmol) for 15 min at room temp. Dimethylamine (~0.2ml) was introduced, and the reaction mixture kept at room temp for 20 min., evaporated to dryness and purified via chromatography (SiO2; acetone/hexanes 4/6 to 8/2) to yield the title compound as colorless foam (59 mg; 64 %).

1H-NMR (400MHz; DMSO-d6), δ (ppm): 1.45(s, 9H); 2.08(bd, 0.5H); 2.18(bt, 1H); 2.25(bd, 0.5H); 2.32(s, 6H); 2.88-3.00(m, 2H); 3.00-3.22(m, 2H); 3.12(s, 2H); 3.28(d, 1H); 3.43(d, 1H); 3.98-4.13(m, 2H); 4.52(bd, 1H); 4.57(bs, 1H); 7.09(t, 2H); 7.20(dd, 1H); 7.30(m, 1H); 7.35(dd, 2H); 7.60(dd, 2H); 7.98(m, 1H); 9.82(s, 1H).

MS (m/z) ES+: 600.1(MH+, 100).

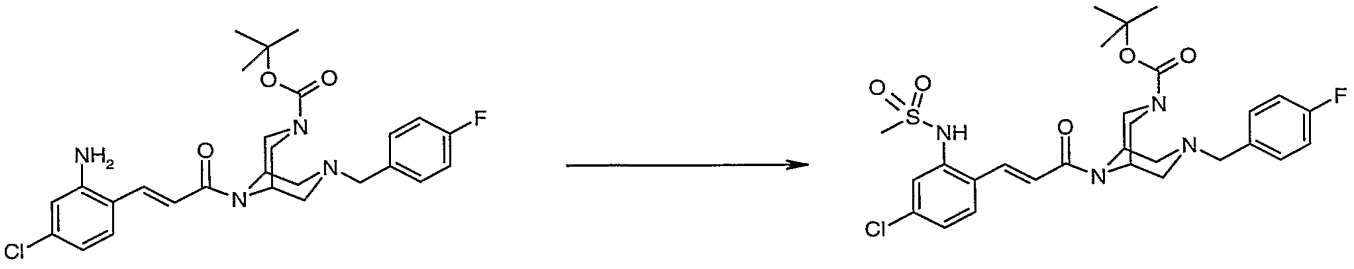
(E)-N-(5-Chloro-2-{3-[3-(4-fluorobenzyl)-3,7,9-triazabicyclo[3.3.1]non-9-yl]-3-oxopropenyl}-phenyl)-2-dimethylaminoacetamide



(E)-9-{3-[4-Chloro-2-(2-dimethylaminoacetylamino)-phenyl]-acryloyl}-7-(4-fluorobenzyl)-3,7,9-triazabicyclo[3.3.1]nonane-3-carboxylic acid tert-butyl ester (55 mg; 0.09 mmol) in CH2Cl2/TFA (1 ml/ 1 ml) was kept at room temp. for 5 min., poured on 2N Na2CO3 / 2N NaOH and extracted with TBME/EtOH (~10:1) three times. The combined organic phases were dried over Na2SO4, filtered and evaporated to dryness. The resulting solid was washed with TBME/hexanes to deliver the target compound as slightly yellow solid (30 mg; 57 %).
1H-NMR (400MHz; DMSO-d6), δ (ppm): 2.28(d, 2H); 2.33(s, 6H); 2.36(d, 2H); 2.73-2.90(m, 2H); 2.97-3.05(m, 2H); 3.11(s, 2H); 3.35(dd, 2H); 4.28(s, 1H); 4.37(s, 1H); 7.12-7.20(m, 3H); 7.28(dd, 1H); 7.36(dd, 2H); 7.60(m, 2H); 7.89(d, 1H); 9.81(s, 1H).
MS (m/z) ES+: 500.2(MH+, 100).

Example 23: (E)-N-(5-Chloro-2-{3-[3-(4-fluorobenzyl)-3,7,9-triazabicyclo[3.3.1]non-9-yl]-3-oxopropenyl}-phenyl)methanesulfonamide

(E)-9-[3-(4-Chloro-2-methanesulfonylamino-phenyl)-acryloyl]-7-(4-fluoro-benzyl)-3,7,9-triazabicyclo[3.3.1]nonane-3-carboxylic acid tert-butyl ester

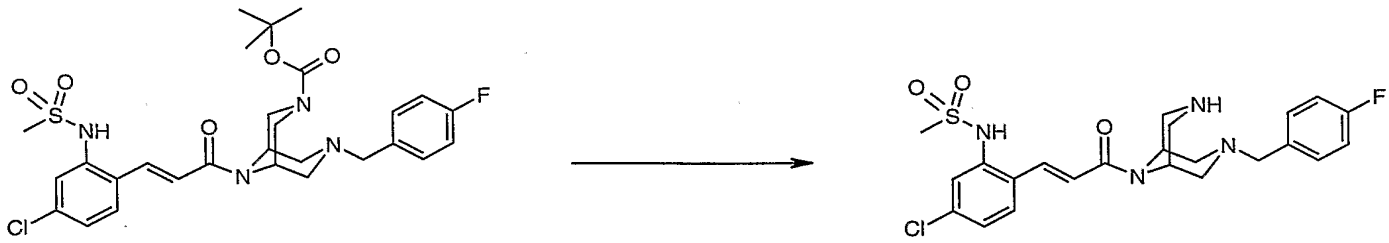


(E)-N-(5-Chloro-2-{3-[3-(4-fluorobenzyl)-3,7,9-triazabicyclo[3.3.1]non-9-yl]-3-oxopropenyl}-phenyl)-acetamide (37 mg; 0.07 mmol) in THF (2 ml) and NEt3 (0.06 ml; 0.43 mmol) was treated with CH3SO2Cl (0.017 ml; 0.21 mmol). After 10 min. at room temp. a second portion of NEt3 (0.06 ml; 0.43 mmol) and CH3SO2Cl (0.017 ml; 0.21 mmol) was added. After 10 min. the reaction poured on EtOH/2N NaOH, kept for 5min. and extracted with TBME three times. The combined organic phases were dried over Na2SO4, evaporated and purified by chromatography (SiO2, TBME/MeOH/NH3conc 90/10/1 then EtOAc/MeOH 8/2) to yield the title compound as yellow foam (15 mg; 35 %).

1H-NMR (400MHz; DMSO-d6), δ (ppm): 1.48(s, 9H); 2.05-2.33(m, 2H); 2.90-3.20(m, 4H); 3.02(s, 3H); 3.30(d, 1H); 3.42(d, 1H); 4.05(dd, 2H); 4.50(bd, 1H); 4.58(bs, 1H); 7.08(t, 2H); 7.18(dd, 1H); 7.32-7.40(m, 4H); 7.83(d, 1H); 7.93(dd, 1H)

MS (m/z) ES+: 593.1(MH+, 100).

<u>(E)-N-(5-Chloro-2-{3-[3-(4-fluorobenzyl)-3,7,9-triazabicyclo[3.3.1]non-9-yl]-3-oxopropenyl}-phenyl)methanesulfonamide</u>

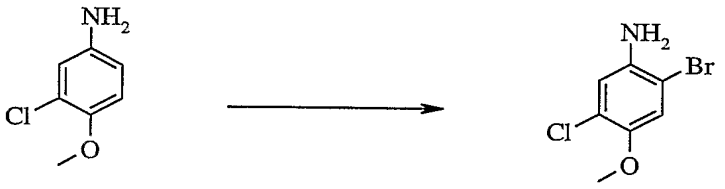


(E)-9-[3-(4-Chloro-2-methanesulfonylamino-phenyl)-acryloyl]-7-(4-fluoro-benzyl)-3,7,9-triazabicyclo[3.3.1]nonane-3-carboxylic acid tert-butyl ester (15 mg; 0.02 mmol) was dissolved in CH2Cl2/TFA (1 ml / 1 ml) and kept at room temp. for 10 min. 2N Na2CO3/2N

NaOH was added and the reaction mixture extracted with TBME/EtOH (~10/1) three times. The combined organic phases were dried over Na2SO4, evaporated and the resulting solid triturated with TBME to yield the title compound as yellowish crystals (7 mg; 58 %).
1H-NMR (400MHz; DMSO-d6), δ (ppm): 2.24-2.42(m, 4H); 2.71(s, 3H); 2.82-3.20(m, 4H); 3.40(dd, 2H); 4.37(s, 1H); 4.51(s, 1H); 7.08(d, 1H); 7.12-7.20(m, 2H); 7.23-7.32(m, 2H); 7.40(dd, 2H); 7.55(d, 1H); 7.93(d, 1H).
MS (m/z) ES+: 494.2(MH+,100).

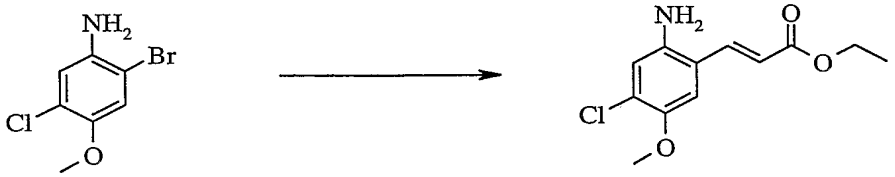
Example 24: 1-(5-Chloro-2-{(E)-3-[3-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1]oct-8-yl]-3-oxopropenyl}-4-methoxyphenyl)-3-methylurea

2-Bromo-5-chloro-4-methoxyphenylamine



NBS (17g; 95.5mmol) in methylene chloride (500 ml) was slowly added to 3-chloro-p-anisidine (15 g; 95.5 mmol) dissolved in methylene chloride (30 ml). After 5min. the reaction mixture was evaporated to half of its volume and treated with hexanes (2000 ml). The resulting precipitate was filtered off and the filtrate evaporated to dryness, taken up in TBME (30 ml) and combined with hexanes (1000 ml). After standing over night the title product crystallized and was filtered off (9.75g; 43%). An additional amount (5.4g; 24%) of product was obtained from the mother liquor after chromatography (SiO2; TBME/hexanes 1:9). Combined yields of title product: 15.15g; 67%.
1H-NMR (400MHz; DMSO-d6), δ (ppm): 3.72 (s, 3H); 5.04 (s, 2H, NH2); 6.87 (s, 1H); 7.13 (s, 1H).
MS (m/z) ES+: 237 (50; M+); 235 (45); 222 (100); 220 (80); 194 (45); 192 (40); 78 (45); 52 (50).

(E)-3-(2-Amino-4-chloro-5-methoxyphenyl)-acrylic acid ethyl ester

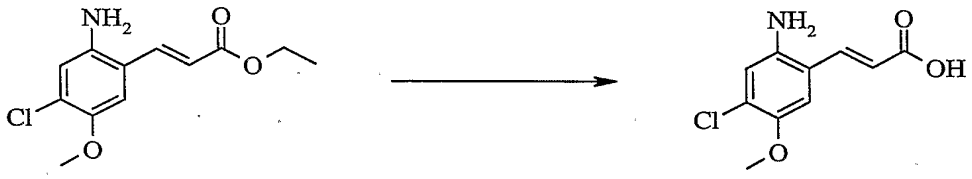


2-Bromo-5-chloro-4-methoxyphenylamine (9.25 g; 39.25 mmol) was dissolved in DMF (100 ml) and combined with ethyl-(E)-3-tributylstannyl)-propenoate (B. Fraser-Reid et al, J. Chem. Soc. Perkin Trans. I, 1994, 1689) (16.8 g; 43 mmol). PdCl2(PPh3)2 (0.55 g; 0.75 mmol) dissolved in warm DMF (50 ml) was added and the reaction mixture heated under argon at 140°C for 20 min. TBME (50ml) and toluene (25ml) were added followed by hexanes (100 ml). The precipitate was filtered off and the filtrate pumped on a silica gel column and purified via chromatography (TBME/hexanes 3:7) yielding the title compound as yellow crystals (8.4 g; 80 %).

1H-NMR (400MHz; DMSO-d6), δ (ppm): 1.25 (t, 3H); 3.77 (s, 3H); 4.16 (q, 2H); 5.42 (s, 2H, NH2); 6.49 (d, 1H); 6.80 (s, 1H); 7.17 (s, 1H); 7.78 (d, 1H).

MS (m/z) ES+: 255 (M+; 55); 210 (100); 194 (45); 166 (55); 138 (40); 104 (55).

(E)-3-(2-Amino-4-chloro-5-methoxyphenyl)-acrylic acid



(E)-3-(2-Amino-4-chloro-5-methoxyphenyl)-acrylic acid ethyl ester (14.87 g; 58.3 mmol) was dissolved in EtOH (450 ml), 2N NaOH (58 ml) added and the reaction mixture refluxed for 10 min. 2N HCl (58 ml) was added, the mixture evaporated to a volume of ~ 100ml, poured on water and extracted with TBME. 10% aqueous acetic acid was added to the aqueous phase and extracted further with TBME. The combined organic phases were dried over Na2SO4, evaporated to dryness and purified via chromatography (SiO2; TBME/hexanes/HOAc 70:30:1) to deliver the title compound (12.3 g; 92 %) as yellow crystals.

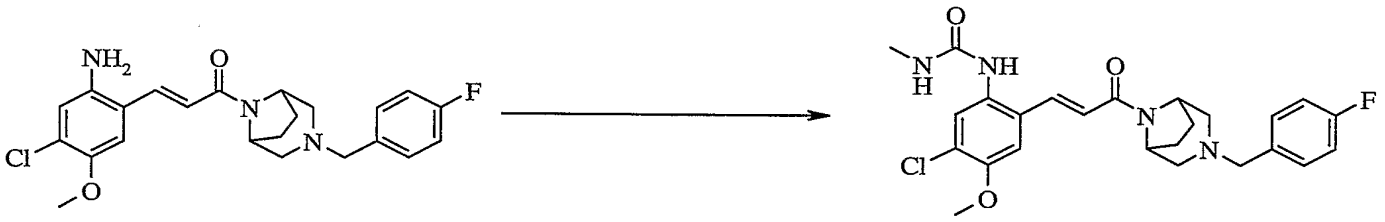
1H-NMR (400MHz; DMSO-d6), δ (ppm): 3.78 (s, 3H); 5.36 (bs, 2H); 6.40 (d, 1H); 6.80 (s, 1H); 7.13 (s, 1H); 7.72 (d, 1H); 12.15 (bs, 1H).

MS (m/z) ES-: 226 (100; MH-).

(E)-3-(2-Amino-4-chloro-5-methoxyphenyl)-1-[3-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1]oct-8-yl]-propenone

(E)-3-(2-Amino-4-chloro-5-methoxyphenyl)-acrylic acid (3 g; 13.2 mmol) and 3-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1]octane (2.9 g; 13.2 mmol) (WO 2002032901) were dissolved in DMF (40ml), combined with HOBt (0.2 g; 1.3 mmol) and EDCI (3 g; 15.8 mmol) and left at room temp. over night. The reaction mixture was poured on water (600 ml) / 10 % HOAc (8 ml) and extracted with TBME three times. The combined organic phases were dried over Na2SO4, evaporated to dryness and purified via chromatography (SiO2; TBME/MeOH/NH3 98:2:0.3) to deliver the title compound (4.9 g; 85 %) as yellow foam.
1H-NMR (400MHz; DMSO-d6), δ (ppm): 1.65-1.75 (m, 1H); 1.83-1.95 (m, 3H); 2.15 (dd, 2H); 2.65 (dd, 2H); 3.45 (s, 2H); 3.75 (s, 3H); 4.50 (bd, 1H); 4. 70 (bd; 1H); 5.25 (bs, 2H, NH2); 6.77 (s, 1H); 6.88 (d, 1H); 7.13 (t, 2H); 7.20 (s, 1H); 7.30 (dd, 2H); 7.65 (d, 1H).
MS (m/z) ES+: 430 (MH+, 100).

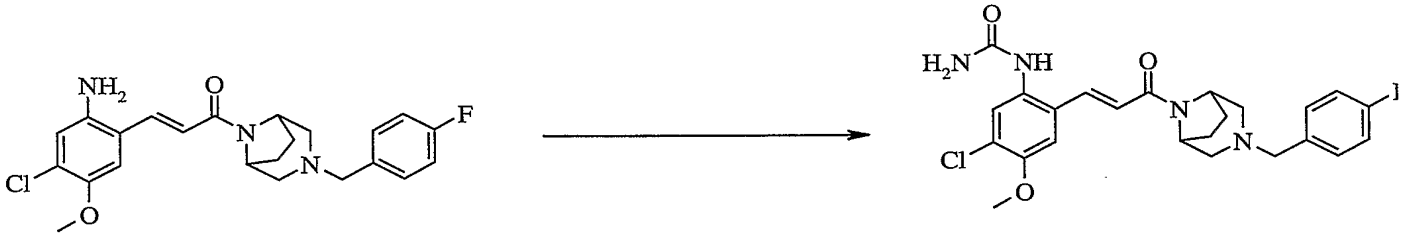
1-(5-Chloro-2-{(E)-3-[3-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1]oct-8-yl]-3-oxopropenyl}-4-methoxyphenyl)-3-methylurea



(E)-3-(2-Amino-4-chloro-5-methoxyphenyl)-1-[3-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1]oct-8-yl]-propenone (4.9 g; 11.4 mmol) was dissolved in THF (250 ml). Triphosgene (3.73 g; 12.6 mmol) was added at room temp. After 7 min. the reaction mixture was placed in a cooling water bath of ~20°C, followed by the addition of an excess of methylamine (~20 ml). After 5min. the reaction mixture was poured on water (1000 ml) and filtered from the precipitated title product. An additional amount of title product was obtained by extracting the aqueous phase with EtOAc three times. The combined organic phases were evaporated. The combined batches of title compound were recrystallised from EtOAc to deliver 1-(5-chloro-2-

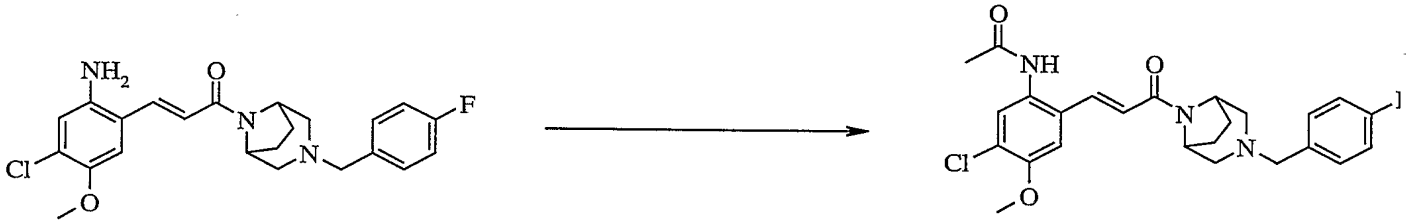
{(E)-3-[3-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1]oct-8-yl]-3-oxopropenyl}-4-methoxyphenyl)-3-methylurea (4.7 g; 86 %) as colorless crystals.
1H-NMR (400MHz; DMSO-d6), δ (ppm): 1.70-1.80 (m, 1H); 1.82-1.98 (m, 3H); 2.17 (dd, 2H); 2.62 (d, 3H); 2.68(dd, 2H); 3.46 (s, 2H); 3.90 (s, 3H); 4.53 (bd, 1H); 4.70 (bd, 1H); 6.27 (q, 1H, NH); 7.05 (d, 1H); 7.13 (dd, 2H); 7.32 (dd, 2H); 7.38 (s, 1H); 7.62 (d, 1H); 7.65 (s, 1H); 8.13 (s, 1H, NH).
MS (m/z) ES+: 487 (100, MH+).

Example 25: (5-Chloro-2-{(E)-3-[3-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1]oct-8-yl]-3-oxopropenyl}-4-methoxyphenyl)-3-urea



(E)-3-(2-Amino-4-chloro-5-methoxyphenyl)-1-[3-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1]oct-8-yl]-propenone (6.5 g; 15.15 mmol) dissolved in HOAc/H2O (90 ml/90 ml) was treated with NaOAc (2.95 g; 45.4 mmol) for 35 min. at room temp. The reaction mixture was poured on a saturated solution of Na2CO3 and extracted with EtOAc three times. The combined organic phases were dried over Na2SO4, evaporated to dryness and purified via chromatography (SiO2; acetone/hexanes 4:6 to 7:3) to yield the title compound (6.24g), which was further purified by recrystallisation from acetone (5.0 g; 69 %) as colorless crystals.
1H-NMR (400MHz; DMSO-d6), δ (ppm): 1.75 (m, 1H); 1.84-2.03 (m, 3H); 2.18 (dd, 2H); 2.68 (dd, 2H); 3.47 (s, 2H); 3.88 (s, 3H); 4.54 (bd, 1H); 4.72 (bd, 1H); 6.03 (s, 2H, NH2); 7.08 (d, 1H); 7.13 (t, 2H); 7.32 (m, 2H); 7.40 (s, 1H); 7.65 (d, 1H); 7.70 (s, 1H); 8.19 (s, 1H, NH).
MS (m/z) ES+: 473 (20, MH+); 430 (100).

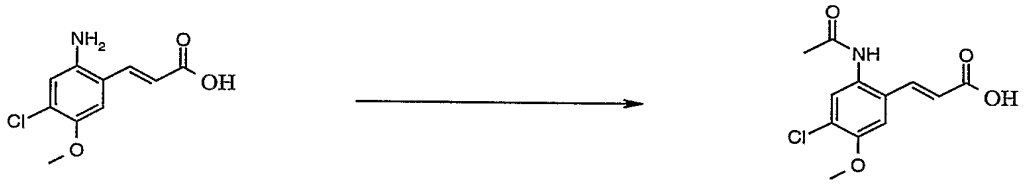
Example 26: N-(5-Chloro-2-{(E)-3-[3-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1]oct-8-yl]-3-oxopropenyl}-4-methoxyphenyl)-acetamide



Acetylchloride (0.83 ml; 1.16 mmol) was added under vigorous stirring to a solution of (E)-3-(2-amino-4-chloro-5-methoxyphenyl)-1-[3-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1]oct-8-yl]-propenone (0.5 g; 1.16 mmol) in THF (10 ml) and NEt3 (1.62 ml; 1.16 mmol). The reaction mixture was poured after 5 min. on a saturated solution of Na2CO3 and extracted with TBME three times. The combined organic phases were dried over Na2SO4, evaporated to dryness and purified via chromatography (SiO2; acetone/hexanes 4:6 to 6:4) to yield the title compound as slightly colored foam (297 mg; 54 %).
1H-NMR (400MHz; DMSO-d6), δ (ppm): 1.75 (m, 1H); 1.83-2.00 (m, 3H); 2.05 (s, 3H); 2.17 (dd, 2H); 2.70 (dd, 2H); 3.48 (s, 2H); 3.93 (s, 3H); 4.53 (bd, 1H); 4.71 (bd, 1H); 7.08-7.17 (m, 3H); 7.32 (dd, 2H); 7.42 (s, 1H); 7.48 (s, 1H); 7.60 (d, 1H); 9.70 (s, 1H).
MS (m/z) ES+: 472 (100, MH+).

Example 27: N-(5-Chloro-2-{(E)-3-[9-(4-fluorobenzyl)-3-oxa-7,9-diazabicyclo[3.3.1]non-7-yl]-3-oxopropenyl}-4-methoxyphenyl)-acetamide

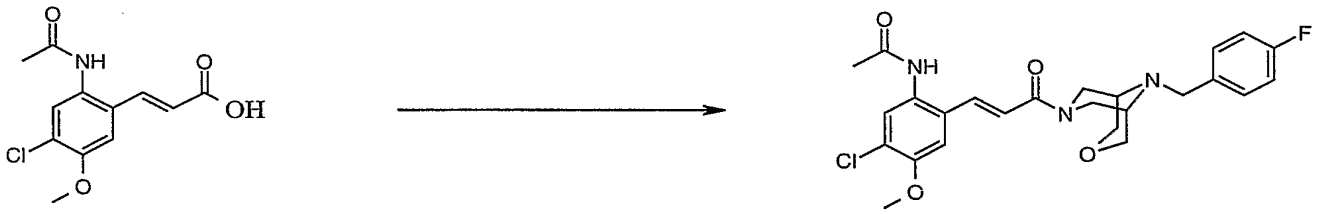
(E)-3-(2-Acetylamino-4-chloro-5-methoxyphenyl)-acrylic acid



(E)-3-(2-Amino-4-chloro-5-methoxyphenyl)-acrylic acid (5 g; 22.0 mmol) was dissolved in pyridine (60 ml) and treated with acetylchloride (1.7 ml; 24.2 mmol) under vigorous stirring at room temp. After 10 min. the reaction mixture was poured on ice-water/HOAc (1000 ml / 60 ml). The precipitated title product was filtered off and the filtrate extracted with EtOAC three times. The combined organic phases were dried over Na2SO4, evaporated to dryness and combined with the first batch of title product. Recrystallisation was carried out by first

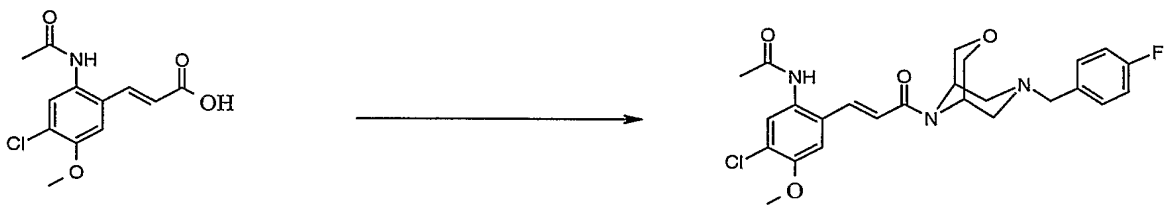
dissolving in acetone/EtOH (1000 ml / 300 ml) followed by evaporation to a volume of ~20 ml. The resulting crystals were washed with acetone and delivered the title acid as pale yellow crystals (4.95 g; 84 %).
1H-NMR (400MHz; DMSO-d6), δ (ppm): 2.08 (s, 3H); 3.91 (s, 3H); 6.65 (d, 1H); 7.45 (s, 2H); 7.62 (d, 1H); 9.74 (s, 1H); 12.5 (bs, 1H).
MS (m/z) ES-: 268 (100, MH-).

N-(5-Chloro-2-{(E)-3-[9-(4-fluorobenzyl)-3-oxa-7,9-diazabicyclo[3.3.1]non-7-yl]-3-oxopropenyl}-4-methoxyphenyl)-acetamide



(E)-3-(2-Acetylamino-4-chloro-5-methoxyphenyl)-acrylic acid (4 g; 14.8 mmol) and 9-(4-fluorobenzyl)-3-oxa-7,9-diazabicyclo[3.3.1]nonane (3.5 g; 14.8 mmol) were dissolved in DMF (90 ml) and combined with EDCI (3.4 g; 17.8 mmol) and HOBt (227 mg; 1.48 mmol) and left over night at room temp. The reaction mixture was poured on 2N HCl. The reaction mixture was then adjusted to ~pH 10 with a saturated solution of Na2CO3 and extracted with TBME/EtOAc three times. The combined organic phases were dried over Na2SO4, evaporated to dryness and purified via chromatography (SiO2; acetone/hexanes 1:1 to 1:0) to yield a colorless foam (6.8g) which was recrystallised from acetone to yield the title compound as colorless crystals (6.3g; 78%).
1H-NMR (400MHz; DMSO-d6), δ (ppm): 2.05 (s, 3H); 2.65 (bs, 2H); 3.65-3.88 (m, 6H); 3.93 (s, 3H); 3.96 (s, 2H); 4.15 (d, 1H); 4.33 (d, 1H); 7.14 (t, 2H); 7.23 (d, 1H); 7.41 (m, 3H); 7.47 (s, 1H); 7.55 (d, 1H); 9.70 (s, 1H).
MS (m/z) ES+: 488 (100, MH+).

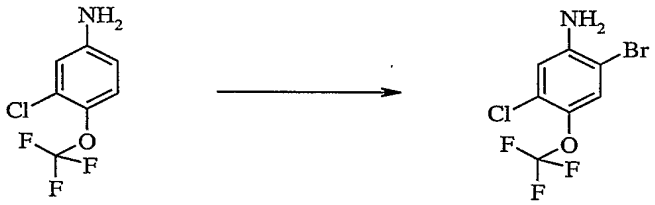
Example 28: N-(5-Chloro-2-{(E)-3-[7-(4-fluorobenzyl)-3-oxa-7,9-diazabicyclo[3.3.1]non-9-yl]-3-oxopropenyl}-4-methoxyphenyl)-acetamide



(E)-3-(2-Acetylamino-4-chloro-5-methoxyphenyl)-acrylic acid (4 g; 14.8 mmol) and 7-(4-fluorobenzyl)-3-oxa-7,9-diazabicyclo[3.3.1]nonane (3.5 g; 14.8 mmol) were dissolved in DMF (90 ml) and combined with EDCI (3.4 g; 17.8 mmol) and HOBt (227 mg; 1.48 mmol) and left over night at room temp. The reaction mixture was poured on 2N HCl. The reaction mixture was then adjusted to ~pH 10 with a saturated solution of Na2CO3 and extracted with TBME/EtOAc three times. The combined organic phases were dried over Na2SO4, evaporated to dryness and purified via chromatography (SiO2; acetone/hexanes 3:7 to 6:4) to yield a colorless foam (6.8g) which was recrystallised from CH2Cl2/THF to yield the title compound as colorless crystals (5.6g; 69 %).
1H-NMR (400MHz; DMSO-d6), δ (ppm): 2.04 (s, 3H); 2.28 (bd, 1H); 2.38 (bd, 1H); 2.98 (dd, 2H); 3.43 (dd, 2H); 3.65 (dd, 2H); 3.88 (bd, 2H); 3.93 (s, 3H); 4.42 (bd, 2H); 7.15 (t, 2H); 7.19 (d, 1H); 7.36 (dd, 2H); 7.44 (s, 1H); 7.48 (s, 1H); 7.65 (d, 1H); 9.72 (s, 1H).
MS (m/z) ES+: 488 (MH+).

Example 29: (5-Chloro-2-{(E)-3-[3-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1]oct-8-yl]-3-oxopropenyl}-4-trifluoromethoxyphenyl)-urea

2-Bromo-5-chloro-4-trifluoromethoxyphenylamine



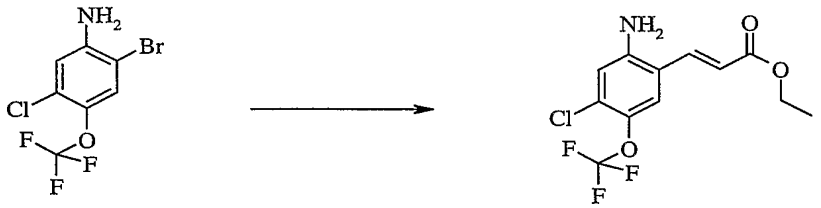
3-Chloro-4-trifluoromethoxyphenylamine (14.4 g; 0.068 mmol) was dissolved in CH2Cl2 (100 ml) and treated with NBS (12.1 g; 0.067 mmol) in CH2Cl2 (500 ml). After 20 min. at room temp. the reaction mixture was evaporated to a volume of ~ 150 ml and combined with hexanes (1000 ml). The precipitate was filtered off and the filtrate purified via

chromatography (SiO2; TBME/hexanes 1:9 to 2:8) to yield the title compound as yellowish crystals (8.4 g; 42 %).

1H-NMR (400MHz; DMSO-d6), δ (ppm): 5.81 (s, 2H, NH2); 6.94 (s, 1H); 7.55 (s, 1H).

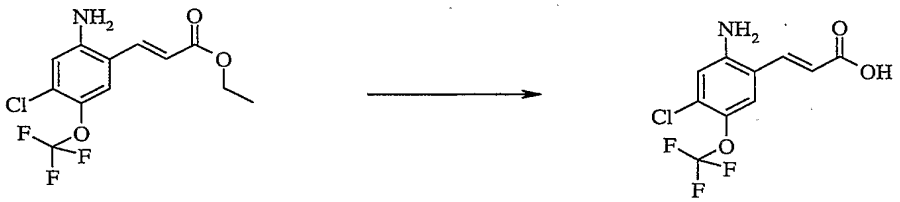
MS (m/z) ES: 290 (100, M+); 288 (85).

(E)-3-(2-Amino-4-chloro-5-trifluoromethoxyphenyl)acrylic acid ethyl ester



2-Bromo-5-chloro-4-trifluoromethoxyphenylamine (2 g; 6.89 mmol) and ethyl-(E)-3-tributylstannyl)-propenoate (3 g; 7.58 mmol) were dissolved in DMF (20 ml). PdCl2(PPh3)2 (0.55 g; 0.75 mmol) dissolved in warm DMF (10 ml) was added and the reaction mixture heated under argon at 140°C for 5 min. TBME (40 ml) and hexanes (60 ml) were added and the reaction mixture poured on a silica gel column and chromatographed (TBME/hexanes 3:7 to 4:6) to render the title compound as yellow crystals (1.65 g; 77 %).

(E)-3-(2-Amino-4-chloro-5-trifluoromethoxyphenyl)acrylic acid

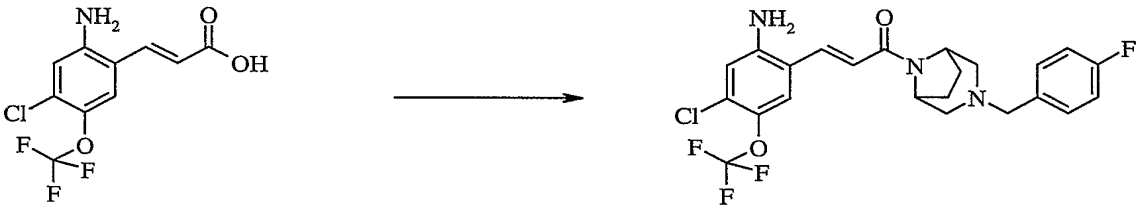


(E)-3-(2-Amino-4-chloro-5-trifluoromethoxyphenyl)acrylic acid ethyl ester (1.65 g; 5.33 mmol) dissolved in EtOH (40 ml) and 2N NaOH (5.3 ml) was refluxed for 10 min. The reaction mixture was diluted with water and washed with TBME. The aqueous phase was acidified with 2N HCl and extracted with TBME three times. The combined organic phases were dried over Na2SO4, evaporated to dryness and yielded the title acid as yellow crystals (1.49 g; 99 %).

1H-NMR (400MHz; DMSO-d6), δ (ppm): 6.05 (s, 2H, NH2); 6.36 (d, 1H); 6.86 (s, 1H); 7.57 (s, 1H); 7.69 (d, 1H); 12.27 (bs, 1H).

MS (m/z) ES-: 280 (100; MH-).

(E)-3-(2-Amino-4-chloro-5-trifluoromethoxyphenyl)-1-[3-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1]oct-8-yl]-propenone

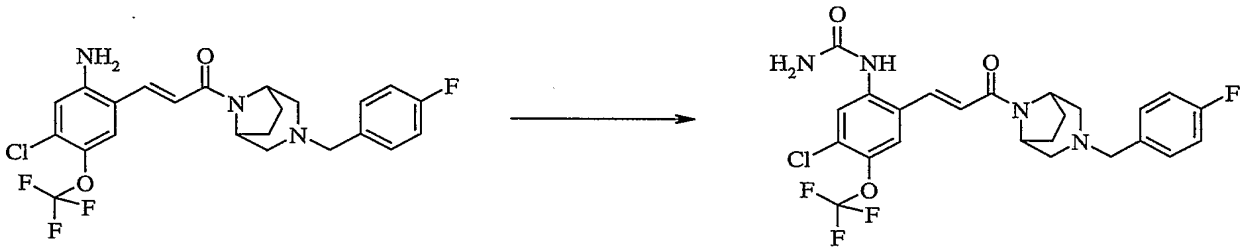


(E)-3-(2-Amino-4-chloro-5-trifluoromethoxyphenyl)acrylic acid (0.40 g; 1.42 mmol) in toluene (30 ml) was treated with 1N HCl in Et2O (2.8 ml; 2.8 mmol). Ether was evaporated and the resulting suspension combined with SOCl2 (6 ml) and refluxed for 10 min. The reaction mixture was evaporated, toluene added and evaporated again to yield (E)-3-(2-amino-4-chloro-5-trifluoromethoxyphenyl)acrylic acid chloride as yellowish crystals. The acid chloride (0.43 g; 1.42 mmol) in toluene (4 ml) and 3-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1]octane in THF (4 ml) were combined and stirred for 10 min. at room temp. The resulting suspension was filtered off, taken up in TBME and washed with a saturated solution of Na2CO3. The organic phase was dried over Na2SO4, evaporated to dryness and purified via chromatography (SiO2, TBME, TBME/MeOH/NH3conc 98:2:0.2) to render the title amide as yellow foam (268 mg; 39 %).

1H-NMR (400MHz; DMSO-d6), δ (ppm): 1.65-1.77 (m, 1H); 1.80-1.95 (m, 3H); 2.15 (dd, 2H); 2.65 (dd, 2H); 3.45 (s, 2H); 4.52 (bd, 1H); 4.65 (bd, 1H); 5.94 (s, 2H, NH2); 6.84 (s, 1H); 6.98 (d, 1H); 7.12 (t, 2H); 7.31 (dd, 2H); 7.56 (d, 1H); 7.69 (s, 1H).

MS (m/z) ES+: 484 (100, MH+).

(5-Chloro-2-{(E)-3-[3-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1]oct-8-yl]-3-oxopropenyl}-4-trifluoromethoxyphenyl)-urea



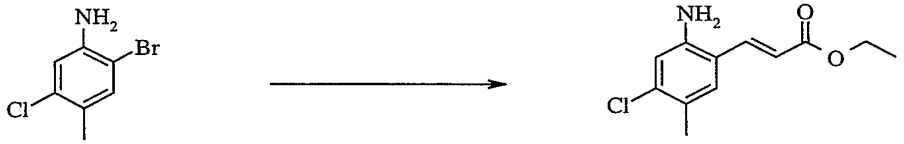
(E)-3-(2-Amino-4-chloro-5-trifluoromethoxyphenyl)-1-[3-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1]oct-8-yl]-propenone (80 mg; 0.166 mmol) was dissolved in HOAc / water (1 ml / 1 ml) and treated with NaOCN (32 mg; 0.496 mmol) for 1h at room temp. The reaction mixture was poured on water and extracted with EtOAc three times. The combined organic phases were dried over Na2SO4, evaporated to dryness and purified via chromatography (SiO2; acetone/hexanes 4:6 to 1:1) to yield the title compound. Recrystallisation from acetone/TBME rendered colorless crystals (37 mg; 43 %).
1H-NMR (400MHz; DMSO-d6), δ (ppm): 1.68-1.78 (m, 1H); 1.82-1.98 (m, 3H); 2.18 (dd, 2H); 2.68 (dd, 2H); 3.45 (s, 2H); 4.53 (bd, 1H); 4.69 (bd, 1H); 6.32 (s, 2H, NH2); 7.12 (m, 3H); 7.29 (m, 2H); 7.60 (d, 1H); 7.94 (s, 1H); 8.13 (s, 1H); 8.54 (s, 1H, NH).
MS (m/z) ES+: 527 (60; MH+); 484 (100).

Example 30: (5-Chloro-2-{(E)-3-[3-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1]oct-8-yl]-3-oxopropenyl}-4-methylphenyl)-urea

2-Bromo-5-chloro-4-methylphenylamine

3-Chloro-4-methylphenylamine (20.0 g; 0.141 mmol) was dissolved in CH2Cl2 (200 ml) and combined within 5 min. with a solution of NBS (25.1 g; 0.141 mmol) in CH2Cl2 (800 ml). The reaction mixture was stirred for 5 min at room temp., evaporated to a volume of ~200 ml and diluted with hexanes (1000 ml). The resulting precipitate was filtered off, the filtrate evaporated to dryness and purified via chromatography (SiO2, hexanes / TBME 10:1) to render the title compound as yellowish crystals (12.3 g; 40 %). A second batch of title compound was obtained by re-chromatography of mixed fractions (7.5 g; 24 %).
1H-NMR (400MHz; DMSO-d6), δ (ppm): 2.13 (s, 3H); 5.32 (s, 2H, NH2); 6.81 (s, 1H); 7.31 (s, 1H).
MS (m/z) ES+: 221 (100, M+); 219 (80); 184 (35); 140 (100); 104 (50); 77 (65); 52 (58); 51 (60).

(2-Amino-4-chloro-5-methylphenyl)-acrylic acid ethyl ester



2-Bromo-5-chloro-4-methylphenylamine (3.0 g; 13.6 mmol) and ethyl-(E)-3-tributylstannyl)-propenoate (6.35 g; 16.3 mmol) were dissolved in DMF (60 ml). PdCl2(PPh3)2 (0.19 g; 0.27 mmol) in DMF (15 ml) was added and the reaction mixture heated to 140°C for 60 min. under argon. The reaction mixture was evaporated and purified via chromatography (SiO2; hexanes / TBME 2:1) to yield the desired compound which was recrystallised from hexanes to yield the title compound as yellow crystals (2.21 g; 68 %).

1H-NMR (400MHz; DMSO-d6), δ (ppm): 1.25 (t, 3H); 2.15 (s, 3H); 4.15 (q, 2H); 5.65 (s, 2H, NH2); 6.38 (d, 1H); 6.75 (s, 1H); 7.43 (s, 1H); 7.77 (d, 1H).

MS (m/z) ES+: 239 (40, M+); 194 (100); 166 (60); 130 (70); 103 (20); 77 (30).

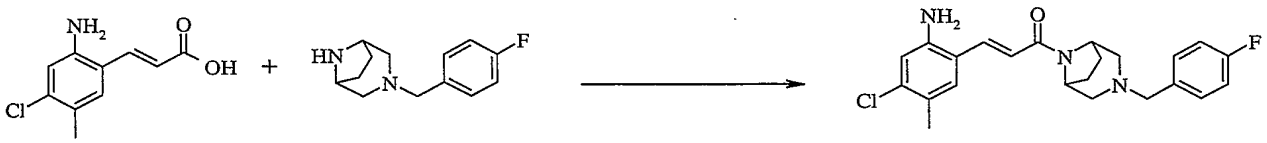
(2-Amino-4-chloro-5-methylphenyl)-acrylic acid

(2-Amino-4-chloro-5-methylphenyl)-acrylic acid ethyl ester (2.21 g; 9.22 mmol) was suspended in EtOH (100 ml) and 2N NaOH (6.9 ml; 13.83 mmol) and kept at 50°C for 45 min. The reaction mixture was diluted with water and extracted with TBME twice. The aqueous phase was acidified with 2N HCl (20 ml) and extracted with TBME three times. The combined organic phases were dried over Na2SO4, filtered and evaporated to dryness to yield the title compound as yellow crystals (1.90 g; 97 %).

1H-NMR (400MHz; DMSO-d6), δ (ppm): 2.17 (s, 3H); 5.60 (s, 2H, NH2); 6.28 (d, 1H); 6.75 (s, 1H); 7.40 (s, 1H); 7.71 (d, 1H); 12.17 (s, 1H).

MS (m/z) ES+: 210 (100, MH-).

(E)-3-(2-Amino-4-chloro-5-methylphenyl)-1-[3-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1]oct-8-yl]-propenone



(2-Amino-4-chloro-5-methylphenyl)-acrylic acid (0.98 g; 4.63 mmol), 3-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1]octane (1.02 g; 4.63 mmol), EDCI (1.06 g; 5.56 mmol) and HOBt (0.07g; 0.46 mmol) in DMF (20 ml) were kept at room temp. over night. The reaction mixture was poured on 20% aqueous HOAc and extracted with TBME three times. The combined organic phases were dried over Na2SO4, evaporated to dryness and purified via chromatography (hexanes / acetone 4:1) to yield the title compound as yellow crystals (1.7 g; 90 %).
1H-NMR (400MHz; DMSO-d6), δ (ppm): 1.65-1.75 (m, 1H); 1.80-1.95 (m, 3H); 2.10-2.20 (m, 2H); 2.15 (s, 3H); 2.60-2.70 (m, 2H); 3.45 (s, 2H); 4.50 (bd, 1H); 4.65 (bd, 1H); 5,46 (s, 2H, NH2); 6.72 (s, 1H); 6.86 (d, 1H); 7.12 (t, 2H); 7.31 (m, 2H); 7.47 (s, 1H); 7.58 (d, 1H).
MS (m/z) ES+: 414 (100, M+).

(5-Chloro-2-{(E)-3-[3-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1]oct-8-yl]-3-oxopropenyl}-4-methylphenyl)-urea

(E)-3-(2-Amino-4-chloro-5-methylphenyl)-1-[3-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1]oct-8-yl]-propenone (1.73 g; 4.18 mmol) in THF (65 ml) was treated with triphosgene (1.24 g; 4.18 mmol) at room temp. under stirring for 10 min. An excess of NH3-gas was introduced, stirring continued for 20 min., the reaction mixture poured on water and extracted with TBME twice. The combined organic phases were dried over Na2SO4, evaporated to dryness and purified via chromatography (SiO2; hexanes / acetone 7:3 to 1:1) to yield the title compound, which contained a considerable amount of undesired bis-urea derivative. Pure title compound (436

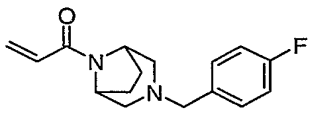
mg; 22 %) was obtained after HPLC-chromatography (Gilson; XTerra; water/ MeOH gradient).

1H-NMR (400MHz; DMSO-d6), δ (ppm): 1.68-1.78 (m, 1H); 1.82-1.97 (m, 3H); 2.15 (dd, 2H); 2.38 (s, 3H); 2.62-2.72 (m, 2H); 3.46 (s, 2H); 4.55 (bd, 1H); 4.67 (bd, 1H); 6.13 (s, 2H, NH2); 7.03 (d, 1H); 7.12 (t, 2H); 7.32 (d, 2H); 7.64 (d, 1H); 7.73 (s, 1H); 7.85 (s, 1H); 8.29 (s, 1H).

MS (m/z) ES+: 457 (100, MH+).

Example 31: 6-(5-Chloro-4-fluoro-2-{(E)-3-[3-(4-fluoro-benzyl)-3,8-diaza-bicyclo[3.2.1]oct-8-yl]-3-oxo-propenyl}-phenyl)-4,6-diaza-spiro[2.4]heptane-5,7-dione

1-[3-(4-Fluoro-benzyl)-3,8-diaza-bicyclo[3.2.1]oct-8-yl]-propenone

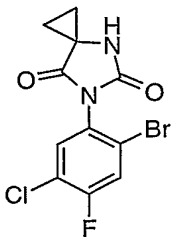


To a solution of 3-(4-fluorobenzyl)-3,8-diazabicyclo[3.2.1]octane (2.0 g, 9.1 mmol) and triethylamine (1.30 ml, 9.1 mmol) in 60 ml dichloromethane was added acryloylchloride (0.74 ml, 9.1 mmol) at 0 °C. After stirring at 0 °C for 90 minutes, the reaction was quenched by addition of NaHCO3 solution, the aqueous phase was extracted with dichloromethane, the organic phase dried over sodium sulfate and the solvent was evaporated. 2.3 g (8.4 mmol, 92%) of crude amide were obtained which were used in the subsequent steps witout further purification.

1H-NMR (400MHz; DMSO-d6), δ (ppm): 1.62-1.95 (m, 4H), 2.10 (dd, 2H), 2.63 (dd, 2H), 3.45 (s, 2H), 4.40-4.50 (m, 2H), 5.65 (dd, 1H), 6.14 (dd, 1H), 6.67 (dd, 1H), 7.12 (t, 2H), 7.31 (dd, 2H).

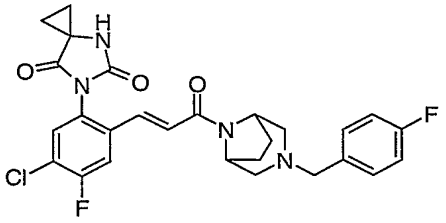
MS (m/z) ESI+: 275 (100, MH+).

6-(2-Bromo-5-chloro-4-fluoro-phenyl)-4,6-diaza-spiro[2.4]heptane-5,7-dione



To a solution of 2-bromo-5-chloro-4-fluoroaniline (0.6 g, 2.7 mmol) and triethylamine (0.93 ml, 6.7 mmol) in 20 ml chloroform was added triphosgene (0.32 g, 1.07 mmol) in one portion. After stirring at room temperature for 5 hours first triethylamine (0.45 ml, 3.2 mmol) then 1-aminocyclopropane-1-carboxylic acid ethyl ester x HCl (0.44g, 2.7 mmol) and the mixture was stirred at 65 °C for 16 hours. The crude product obtained after aquous workup was dissolved in 20 ml dioxane, potassium carbonate (0.37 g, 2.7 mmol) was added and the mixture heated to 120 °C for 16 hours. Addition of water, extraction with ethylacetate, drying and concentration gave the crude hydantoin which was further purified by RP-HPLC to yield 0.69 g (2.1 mmol, 77%) of the title compound.
1H-NMR (400MHz; DMSO-d6), δ (ppm): 1.37 (s, 4H), 7.97 (d, 1H), 8.04 (d, 1H), 8.71 (s, 1H).
MS (m/z) ESI+: 333 (100, MH+).

6-(5-Chloro-4-fluoro-2-{(E)-3-[3-(4-fluoro-benzyl)-3,8-diaza-bicyclo[3.2.1]oct-8-yl]-3-oxo-propenyl}-phenyl)-4,6-diaza-spiro[2.4]heptane-5,7-dione

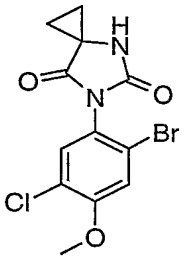


1-[3-(4-Fluoro-benzyl)-3,8-diaza-bicyclo[3.2.1]oct-8-yl]-propenone (136 mg, 0.49 mmol) and 6-(2-Bromo-5-chloro-4-fluoro-phenyl)-4,6-diaza-spiro[2.4]heptane-5,7-dione (150 mg, 0.45 mmol) were dissolved in DMF (4 ml). Triethylamine (0.188 ml, 1.35 mmol), tri-o-tolyl phosphine (14 mg, 0.05 mmol) and palladium acetate (11 mg, 0.05 mmol) were added. The mixture was heated to 120 °C for 3 hours, then poured onto saturated sodium carbonate

solution, extracted into ethylacetate and dried over sodium sulfate. Purification by RP-HPLC (Acetonitrile/Water gradient) gave 56 mg (0.11 mmol, 24%) of the title compound.
1H-NMR (400MHz; DMSO-d6), δ (ppm): 1.38 (s, 4H), 1.67-1.96 (m, 4H), 2.15 (t, 2H), 2.67 (dd, 2H), 3.47 (s, 2H), 4.49 (d, 1H), 4.69 (br s, 1H), 7.13 (t, 2H), 7.16 (d, 1H), 7.26 (d, 1H), 7.31 (dd, 2H), 7.79 (d, 1H), 8.22 (d, 1H), 8.78 (s, 1H).
MS (m/z) ESI+: 527 (100, MH+).

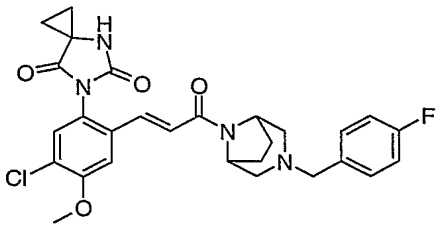
Example 32: 6-(5-Chloro-2-{(E)-3-[3-(4-fluoro-benzyl)-3,8-diaza-bicyclo[3.2.1]oct-8-yl]-3-oxo-ropenyl}-4-methoxy-phenyl)-4,6-diaza-spiro[2.4]heptane-5,7-dione

6-(2-Bromo-5-chloro-4-methoxy-phenyl)-4,6-diaza-spiro[2.4]heptane-5,7-dione



Using the method described in example 31 the title compound was obtained starting from 2-bromo-5-chloro-4-methoxy-aniline in 90% yield.
1H-NMR (400MHz; DMSO-d6), δ (ppm): 1.34 (s, 4H), 3.93 (s, 3H), 7.52 (s, 1H), 7.69 (s, 1H), 8.61 (s, 1H).
MS (m/z) ESI+: 345 (100, MH+).

6-(5-Chloro-2-{(E)-3-[3-(4-fluoro-benzyl)-3,8-diaza-bicyclo[3.2.1]oct-8-yl]-3-oxo-ropenyl}-4-methoxy-phenyl)-4,6-diaza-spiro[2.4]heptane-5,7-dione

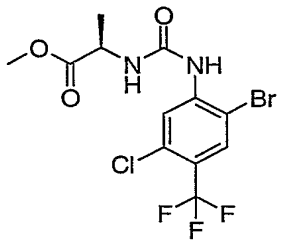


The title compound was prepared as described in example 31. After RP-HPLC purification 42 mg (18%) of the product were obtained.

1H-NMR (400MHz; DMSO-d6), δ (ppm): 1.36 (s, 4H), 1.82-1.95 (m, 4H), 2.20-2.40 (m, 2H), 2.83 (dd, 2H), 3.46 (s, 2H), 3.99 (s, 3H), 4.45-4.52 (m, 1H), 4.67 (br s, 1H), 7.08-7.20 (m, 4H), 7.34 (dd, 2H), 7.54 (s, 1H), 7.61 (s, 1H), 8.67 (s, 1H).
MS (m/z) ESI+: 539 (100, MH+).

Example 33: (R)-3-(5-Chloro-2-{(E)-3-[3-(4-fluoro-benzyl)-3,8-diaza-bicyclo[3.2.1]oct-8-yl]-3-oxo-ropenyl}-4-trifluoromethyl-phenyl)-5-methyl-imidazolidine-2,4-dione

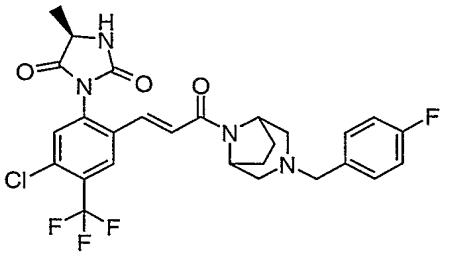
(R)-2-[3-(2-Bromo-5-chloro-4-trifluoromethyl-phenyl)-ureido]-propionic acid methyl ester



To a solution of 2-bromo-5-chloro-4-trifluoromethoxyaniline (0.5 g, 1.8 mmol) and triethylamine (0.63 ml, 4.6 mmol) in 12 ml chloroform was added triphosgene (0.22 g, 0.73 mmol) in one portion. After stirring at room temperature for 5 hours first triethylamine (0.30 ml, 2.2 mmol) then D-alanine methyl ester x HCl (0.25g, 1.8 mmol) was added and the mixture was stirred at 65 °C for 16 hours. The reaction mixture was poured onto sodium bicarbonate solution followed by extraction with ethylacetate, drying and concentration. Chromatography gave 0.34 g (0.9 mmol, 50%) of the title compound.

1H-NMR (400MHz; DMSO-d6), δ (ppm): 1.34 (d, 3H), 3.66 (s, 3H), 4.25 (dq, 1H), 7.94 (d, 1H), 7.99 (s, 1H), 8.42 (s, 1H), 8.48 (s, 1H).
MS (m/z) ESI-: 401 (100, M-H).

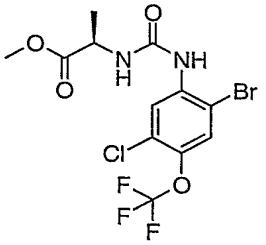
(R)-3-(5-Chloro-2-{(E)-3-[3-(4-fluoro-benzyl)-3,8-diaza-bicyclo[3.2.1]oct-8-yl]-3-oxo-ropenyl}-4-trifluoromethyl-phenyl)-5-methyl-imidazolidine-2,4-dione



1-[3-(4-Fluoro-benzyl)-3,8-diaza-bicyclo[3.2.1]oct-8-yl]-propenone (77 mg, 0.29 mmol) and (R)-2-[3-(2-bromo-5-chloro-4-trifluoromethyl-phenyl)-ureido]-propionic acid methyl ester (100 mg, 0.26 mmol) were dissolved in DMF (4 ml). Triethylamine (0.107 ml, 0.78 mmol), tri-o-tolyl phosphine (8 mg, 0.026 mmol) and palladium acetate (6 mg, 0.026 mmol) were added. The mixture was heated to 120 °C for 16 hours, then poured onto saturated sodium carbonate solution, extracted into ethylacetate and dried over sodium sulfate. Purification by RP-HPLC (Acetonitrile/Water gradient) gave 34 mg (0.06 mmol, 23%) of the title compound.
1H-NMR (400MHz; DMSO-d6), δ (ppm): 1.40 (t, 3H), 1.66-1.95 (m, 4H), 2.15 (t, 2H), 2.67 (dd, 2H), 3.45 (s, 2H), 4.30 (q, 1H), 4.49 (d, 1H), 4.73 (br s, 1H), 7.12 (t, 2H), 7.23 (d, 1H), 7.28-7.34 (m, 3H), 7.88 (d, 1H), 8.42-8.47 (m, 1H), 8.69 (s, 1H).
MS (m/z) ESI+: 565 (100, MH+).

Example 34: (R)-3-(5-Chloro-2-{(E)-3-[3-(4-fluoro-benzyl)-3,8-diaza-bicyclo[3.2.1]oct-8-yl]-3-oxo-propenyl}-4-trifluoromethoxy-phenyl)-5-methyl-imidazolidine-2,4-dione

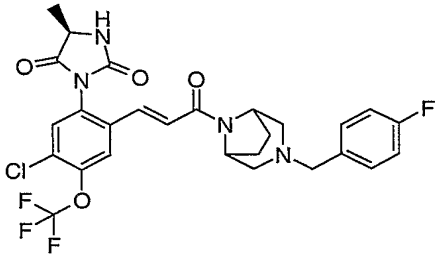
(R)-2-[3-(2-Bromo-5-chloro-4-trifluoromethoxy-phenyl)-ureido]-propionic acid methyl ester



Using the method described in example 33 the title compound was obtained starting from 2-bromo-5-chloro-4-trifluoromethoxy-aniline in 90% yield.
1H-NMR (400MHz; DMSO-d6), δ (ppm): 1.34 (d, 3H), 3.67 (s, 3H), 4.26 (dq, 1H), 7.81 (d, 1H), 7.91 (s, 1H), 8.28 (s, 1H), 8.40 (s, 1H).

MS (m/z) ESI-: 419 (100, M-H).

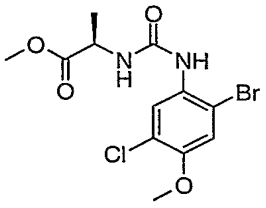
(R)-3-(5-Chloro-2-{(E)-3-[3-(4-fluoro-benzyl)-3,8-diaza-bicyclo[3.2.1]oct-8-yl]-3-oxo-propenyl}-4-trifluoromethoxy-phenyl)-5-methyl-imidazolidine-2,4-dione



The title compound was prepared as described in example 33. After RP-HPLC purification 73 mg (35%) of the product were obtained.
1H-NMR (400MHz; DMSO-d6), δ (ppm): 1.40 (t, 3H), 1.65-1.95 (m, 4H), 2.10-2.19 (m, 2H), 2.65 (dd, 2H), 3.45 (s, 2H), 4.29 (q, 1H), 4.48 (d, 1H), 4.69 (br s, 1H), 7.12 (s, 1H), 7.13 (dd, 2H), 7.27 (d, 1H), 7.30 (dd, 2H), 7.85 (d, 1H), 8.29 (s, 1H), 8.66 (s, 1H).
MS (m/z) ESI+: 581 (100, MH+).

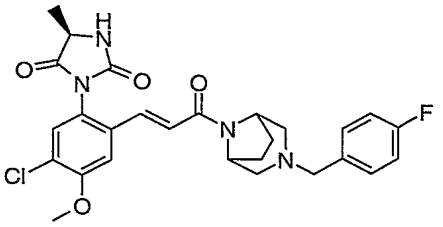
Example 35: (R)-3-(5-Chloro-2-{(E)-3-[3-(4-fluoro-benzyl)-3,8-diaza-bicyclo[3.2.1]oct-8-yl]-3-oxo-propenyl}-4-methoxy-phenyl)-5-methyl-imidazolidine-2,4-dione

(R)-2-[3-(2-Bromo-5-chloro-4-methoxy-phenyl)-ureido]-propionic acid methyl ester



Using the method described in example 33 the title compound was obtained starting from 2-bromo-5-chloro-4-methoxy-aniline in 80% yield.
1H-NMR (400MHz; DMSO-d6), δ (ppm): 1.32 (d, 3H), 3.66 (s, 3H), 3.82 (s, 3H), 4.23 (dq, 1H), 7.35 (s, 1H), 7.45 (d, 1H), 7.96 (s, 1H), 8.04 (s, 1H).
MS (m/z) EI: 364 (100, M+).

(R)-3-(5-Chloro-2-{(E)-3-[3-(4-fluoro-benzyl)-3,8-diaza-bicyclo[3.2.1]oct-8-yl]-3-oxo-propenyl}-4-methoxy-phenyl)-5-methyl-imidazolidine-2,4-dione

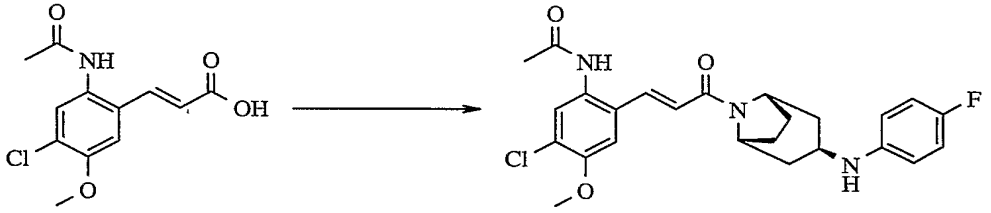


The title compound was prepared as described in example 33. After RP-HPLC purification 51 mg (24%) of the desired product were obtained.

1H-NMR (400MHz; DMSO-d6), δ (ppm): 1.39 (t, 3H), 1.68-1.95 (m, 4H), 2.11-2.22 (m, 2H), 2.68 (dd, 2H), 3.46 (s, 2H), 3.99 (s, 3H), 4.26 (q, 1H), 4.50 (br s, 1H), 4.69 (br s, 1H), 7.08-7.19 (m, 4H), 7.32 (dd, 2H), 7.51 (d, 1H), 7.62 (s, 1H), 8.53 (s, 1H).

MS (m/z) ESI+: 527 (100, MH+).

Example 36: N-(Chloro-2-{(E)-3-[(1S,3R,5R)-3-(4-fluorophenylamino)-8-azabicyclo[3.2.1]oct-8-yl]-3-oxopropenyl}-4-methoxyphenyl)-acetamide



(E)-3-(2-Acetylamino-4-chloro-5-methoxyphenyl)-acrylic acid (100 mg; 0.37 mmol), (1S,3R,5R)-8-azabicyclo[3.2.1]oct-3-yl-(4-fluorophenyl)-amine (WO 2004/009588) (82 mg; 0.37 mmol), EDCI (85 mg; 0.445 mmol) and HOBt (6 mg; 0.037 mmol) were dissolved in DMF (3 ml) and stirred at room temp. over night. The reaction mixture was poured on a saturated solution of Na2CO3 and extracted with TBME three times. The combined organic phases were dried over Na2SO4, evaporated to dryness and purified via chromatography (SiO2, TBME/acetone 20:1). The yellowish crystals were triturated with hot TBME and yielded the pure title compound as colorless crystals (93 mg; 53 %).

1H-NMR (400MHz; DMSO-d6), δ (ppm): 1.75-1.90 (m, 4H); 1.95-2.30 (m, 4H); 2.05 (s, 3H); 3.48 (bm, 1H)); 3.93 (s, 3H); 4.52 (bs, 1H); 4.73 (bs, 1H); 5.60 (bs, 1H); 6.50 (dd, 2H); 6.90 (t, 2H); 7.14 (d, 1H); 7.42 (s, 1H); 7.48 (s, 1H); 7.59 (d, 1H); 9.70 (bs, 1H, NH).
MS (m/z) ES+: 472 (MH+; 100).

Assays:

Preparation of membranes from CHO cells expressing hCCR1:

Membranes were prepared from CHO-K1 cells stably transfected with a plasmid coding for the full-length human CCR1.

Cells were grown in large cell culture dishes (30x30cm) to a confluency of between 80 and 90%(~30x107 cells); in one experiment cells were grown to confluency without loss in receptor density of the membrane preparation.
All subsequent steps to prepare the membranes were performed at 4°C or on ice. After discarding the medium, 30 ml ice-cold PBS containing 1mM EDTA were added and the cells removed from the dishes using a scraper. After centrifugation at 10'000 rpm at 40 °C for 10 minutes in a SS34 rotor the supernatant was discarded and the cells resuspended in 10mL buffer A (20 mM HEPES, 10 mM EDTA, pH 7.4) containing protease inhibitor cocktail (Roche, Complete). The cell suspension was homogenized using a Polytron homogenizer at 28'000 rpm at two intervals of 30 seconds each. In order to collect the membranes the homogenate was centrifuged at 18'000 rpm for 20 minutes at 4 °C using a SS34 rotor. The supernatant was discarded and the pellet resuspended by vortexing in 10 mL buffer B (20 mM HEPES, 0.1 mM EDTA, pH 7.4) containg protease inhibitors followed by a second round of homogenization (2x 30 sec at 28'000rpm, Polytron). After another centrifugation step (20 min at 4 °C, 18'000 rpm) the pellet was resuspended in 5 mL buffer B by vortexing and subsequent homogenization (Polytron, 10 sec).
The protein concentration of the membrane preparation was determined using the BioRAD Protein Assay and human IgG as standard. The protein concentration of the membrane

preparation was adjusted to 1 - 3 mg/mL and either aliquoted into Eppendorf tubes and quickfrozen in liquid nitrogen or, alternatively, the membrane preparation was added dropwise (by a peristaltic pump) into liquid nitrogen where it collects as frozen pellets (50-100 μL) at the bottom of the Dewar vessel. The membranes were stored at –80 °C.

SPA-Binding Assay:

125 μg hCCR1 membranes were thawed and diluted into 340 μl ice-cold Buffer 2 (75 mM HEPES; pH 7.4, 300 mM NaCl, 6 mM $CaCl_2$, 15 mM $MgCl_2$, 1.5 % BSA, Protease inhibitor cocktail (Complete Mini, Roche #61540601), 1 tablet in 10mL). The final volume was adjusted to 1 mL with ice-cold Buffer 3 (20 mM HEPES, 0.1 mM EDTA, pH 7.4). The suspension was homogenized with three strokes and kept on ice.

The assay was performed in a final volume of 200 μl per well in OptiPlate-96well plates. The components were added per well in the following order:

50 μL - CCR1-membranes (2.5μg/well) diluted as described above

50 μL - WGA-SPA beads (1 mg/well) in Buffer 1 (HBSS (1x) (Gibco#1 4025-050), 10 mM HEPES; pH 7.4, 0.1 % BSA (Fluka #05480))

inhibitor diluted in Buffer 1

50 μL - 80 pM [125I]MIP-1α, diluted in Buffer 1 (to give a final concentration of 20 pM in the well)

After the addition of all components the plates were sealed with Top-Seal and incubated at RT for 120 minutes with constant shaking. Following incubation, the plates were centrifuged for 10 minutes at 3000 rpm and counted within 10 hours for 3 minutes per well with a TOP COUNT instrument (Packard).

Compounds of the invention demonstrated inhibition of binding of MIP1α to the human CCR1 receptor with IC50s ranging from 0.1 nM to 1000 nM.

Calcium Flux:

THP-1 cells are cultured in RPMI 1640 medium supplemented with 10 % FCS. The cells are harvested, spun down and resuspended at about 2.106 cells per ml in HBSS 20 mM Hepes in absence of BSA. They are loaded in presence of 2 μM Fluo4 for 30 min at 37°C in a waterbath. After two washes with HBSS 20 mM Hepes, they are resuspended at 0.67x106 cells/ml in the same buffer supplemented with 0.1% BSA and 150 μl containing 105 cells are distributed per well in a black/clear bottom 96-well plate.

The test compounds are prepared from stock solutions at 20 mM in pure DMSO to reach final concentrations ranking 10-5M to 10-11M in HBSS 20 mM Hepes supplemented with 0.1% BSA The agonist rh-MIP-1α is prepared as an eight-fold concentrated solution in the same buffer. Usually a final concentration of 3 nM is used for the screening.

Twenty-five microliters of the compounds are mixed to the 150 μl cells and the plates are let standing for an additional half an hour at RT in the dark to allow cell sedimentation and interaction with the compounds. Then the plate are transferred to the Flexstation (Molecular Devices fluorometer) where the fluo-4 fluorescence of the cells is measured continuously for 2 min in total but after 16 sec. of the base line measurement, 25 μl of the MIP1α solution are injected to the cells at a rate of one (about 26 μl/sec) and a height of 160 μl with two mixing cycles using a volume of 25 μl at a height of 150μl and a rate of one.

The calcium response expressed as the maximal fluorescence in relative fluorescence unit is plotted versus the compound concentration to determine IC_{50} concentrations.

Compounds of the invention demonstrated inhibition of Ca^{2+} mobilisation in response to MIP1α with IC_{50}s ranging from 0.1 nM to 1000 nM

As indicated in the above assays Agents of the Invention potently block the effects of MIP1α, and CCR1. Accordingly, the Agents of the Invention have pharmaceutical utility as follows:

Agents of the Invention are useful for the prophylaxis and treatment of CCR1 or MIP1α mediated diseases or medical conditions. CCR1 and MIP1α play an important role in leukocyte trafficking, in particular in monocyte migration to inflammatory sites and thus the Agents of the Invention may be used to inhibit monocyte migration e.g. in the treatment of inflammatory conditions, allergies and allergic conditions, autoimmune diseases, graft rejection, cancers which involve leukocyte infiltration, stenosis or restenosis, atherosclerosis, rheumatoid arthritis and osteoarthritis.

Diseases or conditions which may be treated with the Agents of the Invention include:
Inflammatory or allergic conditions, including respiratory allergic diseases such as asthma, allergic rhinitis, COPD, hypersensitivity lung diseases, hypersensitivity pneumonitis, interstitial lung disease (ILD), (e.g. idiopathic pulmonary fibrosis, or ILD associated with autoimmune diseases such as RA, SLE, etc.); anaphylaxis or hypersensitivity responses, drug allergies (e.g. to penicillins or cephalosporins), and insect sting allergies; inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis; spondyloarthropathies, sclerodoma; psoriasis and inflammatory dermatoses such as dermatitis, eczema, atopic dermatitis, allergic contact dermatitis, uticaria; vasculitis;
Autoimmune diseases, in particular autoimmune diseases with an aetiology including an inflammatory component such as arthritis (for example rheumatoid arthritis, arthritis chronica progrediente, psoriatic arthritis and arthritis deformans) and rheumatic diseases, including inflammatory conditions and rheumatic diseases involving bone loss, inflammatory pain, hypersensitivity (including both airways hypersensitivity and dermal hypersensitivity) and allergies. Specific autoimmune diseases for which Agents of the Invention may be employed include autoimmune haematological disorders (including e.g. hemolytic anaemia, aplastic anaemia, pure red cell anaemia and idiopathic thrombocytopenia), systemic lupus erythematosus, polychondritis, sclerodoma, Wegener granulomatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, psoriasis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (including e.g. ulcerative colitis, Crohn's disease and Irritable Bowel Syndrome), autoimmune thyroiditis, Behcet's disease, endocrine ophthalmopathy, Graves disease, sarcoidosis, multiple sclerosis, primary biliary cirrhosis, juvenile diabetes (diabetes mellitus type I), uveitis (anterior and posterior), keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, and glomerulonephritis (with and without nephrotic syndrome, e.g. including idiopathic nephrotic syndrome or minimal change nephropathy);
graft rejection (e.g. in transplantation including heart, lung, combined heart-lung, liver, kidney, pancreatic, skin, or corneal transplants) including allograft rejection or xenograft rejection or graft-versus-host disease, and organ transplant associated arteriosclerosis; atherosclerosis;
cancer with leukocyte infiltration of the skin or organs;
stenosis or restenosis of the vasculature, particularly of the arteries, e.g. the coronary artery, including stenosis or restenosis which results from vascular intervention, as well as neointimal hyperplasia;

and other diseases or conditions involving inflammatory responses including reperfusion injury, hematologic malignancies, cytokine induced toxicity (e.g. septic shock or endotoxic shock), polymyositis, dermatomyositis, and granulomatous diseases including sarcoidosis.

Furthermore, the compounds pass the blood-brain barrier. Accordingly, the Agents of the Invention containing a radioisotope have pharmaceutical utility as markers in neuroimaging, for example in the treatment diagnosis of diseases such as Alzheimer's disease.

The term "treatment" as used herein is to be understood as including both therapeutic and prophylactic modes of therapy e.g. in relation to the treatment of neoplasia, therapy to prevent the onset of clinically or preclinically evident neoplasia, or for the prevention of initiation of malignant cells or to arrest or reverse the progression of premalignant to malignant cells, as well as the prevention or inhibition of neoplasia growth or metastasis. In this context, the present invention is, in particular, to be understood as embracing the use of compounds of the present invention to inhibit or prevent development of skin cancer, e.g. squamus or basal cell carcinoma consequential to UV light exposure, e.g. resultant from chronic exposure to the sun.

Agents of the Invention are particularly useful for treating diseases of bone and cartilage metabolism including osteoarthritis, osteoporosis and other inflammatory arthritides, e.g. rheumatoid arthritis, and bone loss in general, including age-related bone loss, and in particular periodontal disease.

The Agents of the Invention may also be used in ocular applications which include the treatment of ocular disorders, in particular of ocular inflammatory disorders, of ocular pain including pain associated with ocular surgery such as PRK or cataract surgery, of ocular allergy, of photophobia of various etiology, of elevated intraocular pressure (in glaucoma) by inhibiting the production of trabecular meshwork inducible glucocorticoid response (TIGR) protein, and of dry eye disease.

For the above indications, the appropriate dosage will, of course, vary depending upon, for example, the particular Agent of the Invention to be employed, the subject to be treated, the mode of administration and the nature and severity of the condition being treated. However, in prophylactic use, satisfactory results are generally indicated to be obtained at dosages

from about 0.01 mg to about 10 mg, more preferably from about 0.05 mg to about 10 mg per kilogram body weight. Agent of the Invention is conveniently administered orally, parenterally, intravenously, e.g. into the antecubital or other peripheral vein, intramuscularly, or subcutaneously. For example, treatment typically comprises administering the Agent of the Invention once daily up to 3 times a day.

Pharmaceutical compositions of the invention may be manufactured in conventional manner The Agents of the Invention may be administered by any conventional route, e.g. orally, for example in the form of solutions for drinking, tablets or capsules or parenterally, for example in the form of injectable solutions or suspensions. Normally for systemic administration oral dosage forms are preferred, although for some indications the Agents of the Invention may also be administered topically or dermally, e.g. in the form of a dermal cream or gel or like preparation or, for the purposes of application to the eye, in the form of an ocular cream, gel or eye-drop preparation; or may be administered by inhalation, e.g., for treating asthma. Suitable unit dosage forms for oral administration comprise e.g. from 25 to 1000mg of Agent of the Invention per unit dosage.

In accordance with the foregoing the present invention also provides in a further series of embodiments:

A. A method of inhibiting Chemokine Receptor 1 (CCR-1) or of reducing inflammation in a subject (i.e., a mammal, especially a human) in need of such treatment which method comprises administering to said subject an effective amount of an Agent of the Invention, or a method of treating any of the above mentioned conditions, particularly a method of treating an inflammatory or autoimmune disease or condition, e.g. rheumatoid arthritis, or alleviating one or more symptoms of any of the above mentioned conditions.

B. An Agent of the Invention for use as a pharmaceutical, e.g. for use as an immunosuppressant or antiinflammatory agent or for use in the prevention, amelioration or treatment of any disease or condition as described above, e.g., an autoimmune or inflammatory disease or condition.

C. A pharmaceutical composition comprising an Agent of the Invention in association with a pharmaceutically acceptable diluent or carrier, e.g., for use as an immunosuppressant or anti-inflammatory agent or for use in the prevention, amelioration or treatment of any disease or condition as described above, e.g., an autoimmune or inflammatory disease or condition.

D. Use of an Agent of the Invention in the manufacture of a medicament for use as an immunosuppressant or anti-inflammatory agent or for use in the prevention, amelioration or treatment of any disease or condition as described above, e.g., an autoimmune of inflammatory disease or condition.

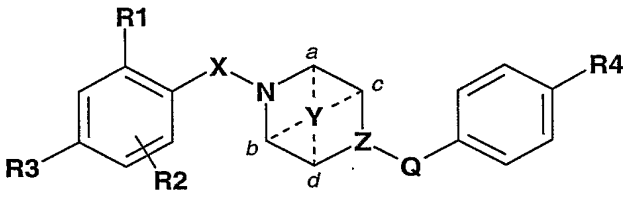
E. An Agent of the Invention containing a radiolabel for use as a marker in neuroimaging, for example in the diagnosis of Alzheimer's disease.

F. Use of an Agent of the Invention containing a radiolabel as a marker in neuroimaging, for example in the diagnosis of Alzheimer's disease.

G. Use of an Agent of the Invention containing a radiolabel in the manufacture of a medicament for the diagnosis of Alzheimer's disease.

CLAIMS

1. A compound of formula I, or a pharmaceutically acceptable salt or ester thereof,



I

wherein

R1, R2 and R3 are independently selected from the group consisting of hydrogen, cyano, halo, nitro or optionally substituted oxy, lower alkyl, lower alkyenyl, lower alkynyl, carbonyl, amino, sulfur, cycloalkyl, heterocycloalkyl, aryl, heteroaryl or a substituent forming a bicyclic ring system of which the phenyl ring to which it is attached forms part of the bicycle for example butadiene forming napthyl, or heterobutadiene forming quinolinyl, quinoxalinyl or isoquinolinyl;

R4 is selected from the group consisting of hydrogen, cyano, halo, nitro or optionally substituted oxy, lower alkyl, lower alkyenyl, lower alkynyl, carbonyl, amino, sulfur, cycloalkyl, heterocycloalkyl, aryl, heteroaryl or a substituent forming a bicyclic ring system of which the phenyl ring to which it is attached forms part of the bicycle for example butadiene forming napthyl, or heterobutadiene forming quinolinyl, quinoxalinyl or isoquinolinyl;

X is –CH=CHCO-, -OCH_2CO- or –$NHCH_2CO$-;

Y is –$(CH_2)_n$- where n is 1-6, -CH_2OCH_2- or -CH_2NRCH_2- and is bonded to two of the ring carbon atoms, bonding being to either the ring carbon atoms *a* and *b* or the ring carbon atoms *c* and *d*;

wherein R is selected from the group consisting of H, optionally substituted: lower alkyl, carbonyl, acyl, acetyl or sulfonyl;

Z is N or –CH-;

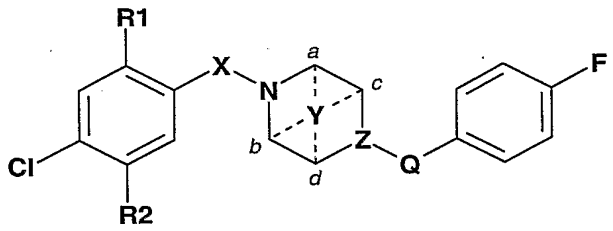
Q is -CH_2-, -NH- or -O-;

wherein when Z is N, Q is CH_2, and when Z is –CH-, Q is –NH- or –O-;

with the proviso that when Y is –$(CH_2)_n$- and when Z is N, X is –CH=CHCO-;
and the proviso that when Q is NH or O and when X is -OCH_2CO- or –$NHCH_2CO$- and when Y is –$(CH_2)_n$ or -CH_2OCH_2-, Y is bonded to ring carbon atoms *c* and *d*

Wherein the optional substituents on R1-R4 are one or more, e.g. 1-3 substituents, independently selected from the group consisting of hydrogen, oxo, cyano, halo, nitro or optionally substituted oxy, lower alkyl, lower alkyenyl, lower alkynyl, amino, sulfur, sulfinyl, sulfonyl;
wherein the optionally substituted substituents are optionally substituted once or more by, e.g. 1-6 substituents, a substituent independently selected from the group consisting of hydrogen, oxo, cyano, halo, nitro, oxy, lower alkyl, lower alkyenyl, lower alkynyl, amino, sulfur, cycloalkyl, heterocyloalkyl, aryl.

2. A compound of formula II:



II

wherein R1, R2, X, N, Y, Z and Q are as defined above with respect to formula I.

3. A compound of formula I wherein the compound includes a radioisotope selected from the group of ^{11}C, ^{18}F, ^{75}Br, ^{76}Br, ^{80}Br, ^{123}I, ^{125}I, ^{128}I, ^{131}I, ^{13}N , ^{15}O.

4. A compound according to any one of claims 1-3 for use as a pharmaceutical.

5. A compound according to any one of claims 1-2 for use in the treatment of inflammation.

6. A compound according to any one of claim 3 for use as a marker in neuroimaging.

7. A method of inhibiting chemokine receptors or of reducing inflammation in a mammal in need of such treatment which method comprises administering to said subject an effective amount of a compound according to claim 1 or claim 2.

8. Use of a compound according to any one of claims 1-13 as a marker in neuroimaging.

9. A pharmaceutical composition comprising a compound according to claim 1 or 2 in association with a pharmaceutically acceptable diluent or carrier, for use as an immunosuppressant or anti-inflammatory agent.

10. Use of a compound according to claim 1 or 2 in the manufacture of a medicament for for use as an immunosuppressant or anti-inflammatory agent or for use in the prevention, amelioration or treatment of an autoimmune of inflammatory disease or condition.

11. Use of a compound according to claim 3 in the manufacture of a medicament for the diagnosis of Alzheimer's disease.

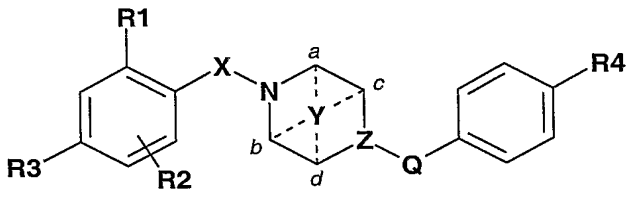
12. A pharmaceutical composition comprising a compound according to claim 3 in association with a pharmaceutically acceptable diluent or carrier, for use as a marker in neuroimaging.

13. A process for the preparation of a compound of formula I.

14. All novel compounds, methods, processes and uses substantially as hereinbefore described with particular reference to the Examples.

Abstract

A compound of formula I, or a pharmaceutically acceptable salt or ester thereof,



(I)

wherein the symbols have meaning as defined, which are antagonists of CCR-1 and which find use pharmaceutically for treatment of diseases and conditions in which CCR-1 is implicated, e.g. inflammatory diseases.